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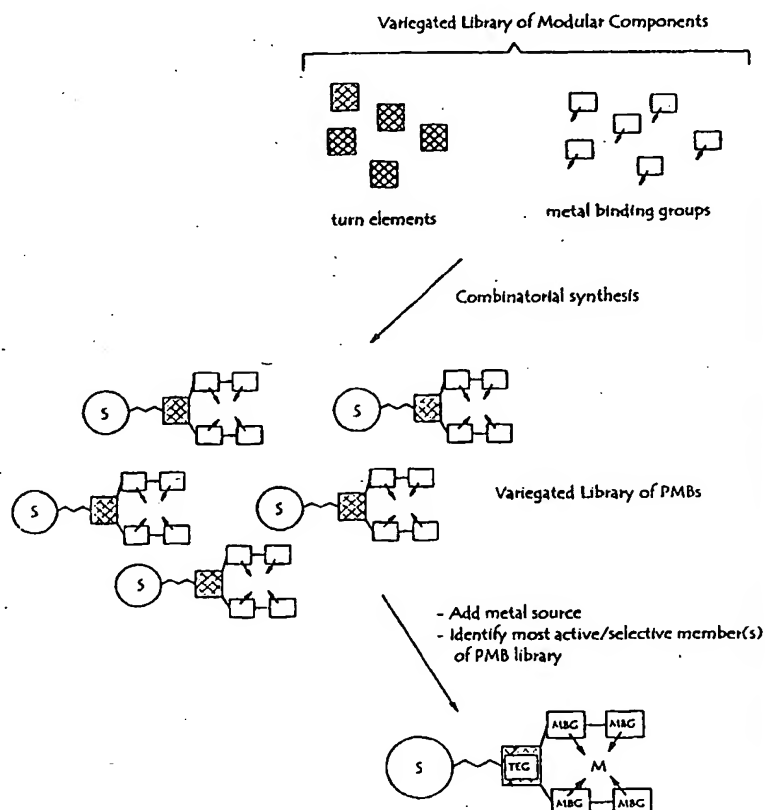
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: COMBINATORIAL APPROACH FOR GENERATING NOVEL COORDINATION COMPLEXES

## (57) Abstract

The present invention provides methods and compositions, i.e. synthetic libraries of binding moieties, for identifying compounds which bind to a metal atom or to non-metal ions, e.g., cationic or anionic molecules.



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## AMENDED CLAIMS

[received by the International Bureau on 12 March 1998 (12.03.98);  
new claims 32-74 added; remaining claims unchanged (10 pages)]

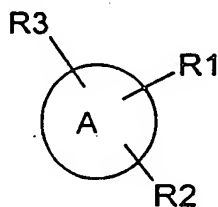
1. A method for identifying a chelating agent for a metal or ion, comprising
  - (a) chemically synthesizing a variegated library of potential binding moieties (PBMs) from a variegated assortment of metal binding groups (MBGs) bearing Lewis basic atoms and turn elements, the PBMs of the PBM library having at least one turn element substituted at least twice with MBGs; and
  - (b) isolating PBMs from the PBM library on the basis of ability to bind to a metal or ion.
2. The method of claim 1, wherein the turn element is has a reduced number of internal rotational bonds.
3. The method of claim 1, wherein the turn element is a carbocycle or heterocycle.
4. The method of claim 3, wherein the turn element is selected from the group consisting of a monocyclic ring and a polycyclic ring.
5. The method of claim 3, wherein the turn element is selected from the group consisting of acridarsine, acridine, anthracene, arsindole, arsinoline, azepane, benzene, carbazole, carboline, chromene, cinnoline, furan, furazan, hexahydropyridazine, hexahydropyrimidine, imidazole, indane, indazole, indole, indolizine, isoarsindole, isobenzofuran, isochromene, isoindole, isophosphindole, isophosphinoline, isoquinoline, isorasinoline, isothiazole, isoxazole, morpholine, naphthalene, naphthyridine, oxazole, oxolane, perimidine, phenanthrene, phenanthridine, phenanthroline, phenarsazine, phenazine, phenomercurazine, phenomercurin, phenophosphazine, phenoselenazine, phenotellurazine, phenothiarsine, phenoxantimonin, phenoxaphosphine, phenoxarsine, phenoxaselenin, phenoxatellurin, phenothiazine, phenoxathiin, phenoxazine, phosphanthene, phosphindole, phosphinoline, phthalazine, piperazine, piperazine, piperidine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrolidine, pyrrolidine, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, selenanthrene, selenophene, tellurophene, tetrahydrofuran, tetrahydrothiophene, thianthrene, thiazole, thiolane, thiophene and xanthene.
6. The method of claim 3, wherein the turn element is a bicyclo[x.y.z]alkane, where x, y and z are each integers of 1 or greater.
7. The method of claim 6, wherein the bicyclo[x.y.z]alkane, is selected from the group consisting of 2-methylbicyclo[2.1.0]pentane, bicyclo[2.1.1]hexane, 1,4-dimethylbicyclo [2.2.0]hexane, bicyclo[2.2.1]heptane (norbornane), 7,7-dimethylbicyclo[2.2.1]heptane, endo-2-Isopropyl-7,7-dimethylbicyclo[2.2.1]heptane.

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- trans-bicyclo[4.4.0]decan-3-one, bicyclo[2.2.2]octane, 1,4-diisopropylbicyclo[2.2.2]octane, (2S,3S)-2-ethyl-3-methyl-bicyclo[2.2.2]octane, bicyclo[3.1.0]hexane, 2,6,6-Trimethylbicyclo[3.1.1]heptane. bicyclo-[3.2.0]heptane, bicyclo[3.2.2]nonane, bicyclo[3,3,0]octane, 1,2-dimethylbicyclo-[3.3.0]octane, 5 bicyclo[3.3.3]undecane, bicyclo[4.1.0]heptane, (1S,2R,4S,6R)-4-Ethyl-2-isopropylbicyclo[4.1.0]heptane, cis-bicyclo[4.2.1]nonane, 1,9-Dimethylbicyclo[4.2.1]nonane, trans-1,6-dibromobicyclo[4,3,0]nonane, 1-Methyl-8-propylbicyclo[4.3.0]nonane, bicyclo[4.3.2]undecane, cis-bicyclo[4.4.0]decane (cis-Decalin), trans-bicyclo[4.4.0]decane (trans-Decalin), and trans-Bicyclo[4.4.0]decan-3-one.
- 10 8. The method of claim 3, wherein the turn element is a bridged heterocycle.
  9. The method of claim 3, wherein the turn element is a caged polycycle.
  10. The method of claim 9, wherein the caged polycycle is selected from the group consisting of adamantane, diamantane, cubane and quadricyclene.
  11. The method of claim 3, wherein the turn element is a saccharide.
  - 15 12. The method of claim 11, wherein the saccharide is a mono-, di- or trisaccharide.
  13. The method of claim 11, wherein the saccharide is a pentose or hexose sugar, or pentose or hexose azasugar.
  14. The method of any of claims 1-13, wherein at least one turn element provided in the PBM library is a chiral turn element.
  - 20 15. The method of claim 14, wherein the PBM library includes at least two stereoisomers of a chiral turn elements.
  16. The method of claim 15, wherein the stereoisomers are enantiomeric chiral turn elements.
  - 25 17. The method of claim 15, wherein the stereoisomers are diastereomeric chiral turn elements.
  18. The method of any of claims 1-13, wherein the PBM library is variegated with respect to turn elements incorporated in the individual PBMs.
  19. The method of claim 1, wherein PBM library includes MBGs having one or more Lewis basic atoms.
  - 30 20. The method of claim 19, wherein the Lewis basic groups atoms are selected from Group 15 and Group 16 atoms.
  21. The method of claim 19, wherein the Lewis basic groups atoms are selected from Nitrogen, Oxygen, Phosphorous and Sulfur.

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22. The method of claim 19, wherein the MBGs are selected from the group consisting of amines (primary, secondary, and tertiary), aromatic amines, amino groups, amido groups, nitro groups, nitroso groups, amino alcohols, nitriles, isonitriles, cyanates, isocyanates, imino groups, phosphates, phosphonates, phosphites, substituted and unsubstituted phosphines, phosphine oxides, phosphorothioates, phosphoramidates, phosphonamidites, hydroxyls, carbonyls (e.g., carboxyl, ester and formyl groups), aldehydes, ketones, ethers, carbamoyl groups, thiols, sulfides, thiocarbonyls (e.g., thiolcarboxyl, thiolester and thiolformyl groups), thioethers, mercaptans, sulfonic acids, sulfates, sulfonates, sulfonones, sulfonamides, sulfamoyls and sulfinyls.
23. The method of claim 1, wherein the PBM library is immobilized on an insoluble matrix.
24. The method of claim 1, wherein PBMs are isolated from the PBM library on the basis of ability to bind to a metal.
25. The method of claim 24, wherein the metal is a transition metal.
26. The method of claim 24, wherein the metal is a Lanthanide metal.
27. The method of claim 24, wherein the metal is selected from the group consisting of  $\text{Co}^{3+}$ ,  $\text{Cr}^{3+}$ ,  $\text{Hg}^{2+}$ ,  $\text{Pd}^{2+}$ ,  $\text{Pt}^{2+}$ ,  $\text{Pd}^{4+}$ ,  $\text{Pt}^{4+}$ ,  $\text{Rh}^{3+}$ ,  $\text{Ir}^{3+}$ ,  $\text{Ru}^{3+}$ ,  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Fe}^{2+}$ ,  $\text{Au}^{3+}$ ,  $\text{Au}^{+}$ ,  $\text{Ag}^{+}$ ,  $\text{Cu}^{+}$ ,  $\text{MO}_2^{2+}$ ,  $\text{Ti}^{3+}$ ,  $\text{Bi}^{3+}$ ,  $\text{CH}_3\text{Hg}^{+}$ ,  $\text{Al}^{3+}$ ,  $\text{Ga}^{3+}$ ,  $\text{Ce}^{3+}$ ,  $\text{UO}_2^{2+}$ , and  $\text{La}^{3+}$ .
28. The method of claim 1, wherein the PBM library includes at least  $10^2$  different PBM species.
29. A method for identifying a chelating agent for a metal or ion, comprising  
(a) chemically synthesizing a variegated library of potential binding moieties (PBMs) represented by the general formula:



wherein

A represents a carbocycle or heterocycle which can be monocyclic or polycyclic, aromatic or non-aromatic;

R1 and R2 each represent, independently for each occurrence in a PBM of the PBM library, an MPG including a moiety selected from the group consisting of

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amines (primary, secondary, and tertiary and aromatic amines), amino groups, amido groups, nitro groups, nitroso groups, amino alcohols, nitriles, imino groups, phosphates, phosphonates, phosphites, (substituted) phosphines, phosphine oxides, phosphorothioates, phosphoramidates, phosphonamidites, hydroxyls, carbonyls (e.g., carboxyl, ester and formyl groups), aldehydes, ketones, ethers, carbamoyl groups, thiols, sulfides, thiocarbonyls (e.g., thiolcarboxyl, thiolester and thiolformyl groups), thioethers, mercaptans, sulfonic acids, sulfates, sulfonates, sulfonones, sulfonamides, sulfamoyls and sulfinyls, or alkyl, alkenyl or alkynyl groups (preferably in the range of C<sub>1</sub>-C<sub>30</sub>) substituted therewith;

R3 is absent or represents one or more further MPG substitutions to the ring A, each occurrence of which independently includes a moiety selected from the group consisting of amines (primary, secondary, and tertiary and aromatic amines), amino groups, amido groups, nitro groups, nitroso groups, amino alcohols, nitriles, imino groups, phosphates, phosphonates, phosphites, (substituted) phosphines, phosphine oxides, phosphorothioates, phosphoramidates, phosphonamidites, hydroxyls, carbonyls (e.g., carboxyl, ester and formyl groups), aldehydes, ketones, ethers, carbamoyl groups, thiols, sulfides, thiocarbonyls (e.g., thiolcarboxyl, thiolester and thiolformyl groups), thioethers, mercaptans, sulfonic acids, sulfates, sulfonates, sulfonones, sulfonamides, sulfamoyls and sulfinyls, or alkyl, alkenyl or alkynyl groups (preferably in the range of C<sub>1</sub>-C<sub>30</sub>) substituted therewith

(b) isolating PBMs from the PBM library on the basis of ability to bind to a metal or ion.

30. A library of potential metal binding ligands comprising at least one turn element represented by the general formula: T-R1(-R2)(-R3), wherein T is a turn element, R1 and R2 are, individually, substituents of turn element T each having at least one Lewis basic moiety for binding to a metal atom, and R3 is absent or represents one or more substituents of T each having at least one Lewis basic moiety for binding to a metal atom.

31. A chelating agent identified according to the method of claim 1 or 29.

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32. A method for generating an organo-metallic catalyst, comprising
- (a) chemically synthesizing a variegated library of potential binding moieties (PBMs) from a variegated assortment of metal binding groups (MBGs) bearing Lewis basic atoms and turn elements, the PBMs of the PBM library having at least one turn element substituted at least twice with MBGs; and
  - (b) contacting the PBM library, during or after its synthesis, with one or more metals under conditions wherein PBMs able to bind to the metal form PBM-metal complexes
  - (c) determining the ability of the PBM-metal complexes to catalyze a reaction.
33. The method of claim 32, wherein the turn element has a reduced number of internal rotatable bonds.
34. The method of claim 32, wherein the turn element is a carbocycle or heterocycle.
35. The method of claim 34, wherein the turn element is selected from the group consisting of a monocyclic ring and a polycyclic ring.
36. The method of claim 34, wherein the turn element is selected from the group consisting of acridarsine, acridine, anthracene, arsindole, arsinoline, azepane, benzene, carbazole, carboline, chromene, cinnoline, furan, furazan, hexahydropyridazine, hexahydropyrimidine, imidazole, indane, indazole, indole, indolizine, isoarsindole, isobenzofuran, isochromene, isoindole, isophosphindole, isophosphinoline, isoquinoline, isorasinoline, isothiazole, isoxazole, morpholine, naphthalene, naphthyridine, oxazole, oxolane, perimidine, phenanthrene, phenanthridine, phenanthroline, phenarsazine, phenazine, phenomercurazine, phenomercurin, phenophosphazine, phenoselenazine, phenotellurazine, phenothiarsine, phenoxantimonin, phenoxaphosphine, phenoxarsine, phenoxaselenin, phenoxatellurin, phenothiazine, phenoxathiin, phenoxazine, phosphanthene, phosphindole, phosphinoline, phthalazine, piperazine, piperidine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrolidine, pyrrolidine, pyrrolizine, quinazoline, quinoline, quinolizine,

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quinoxaline, selenanthrene, selenophene, tellurophene, tetrahydrofuran, tetrahydrothiophene, thianthrene, thiazole, thiolane, thiophene and xanthene.

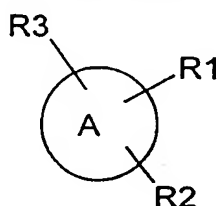
37. The method of claim 34, wherein the turn element is a bicyclo[x.y.z]alkane, where x, y and z are each integers of 0 or greater.
38. The method of claim 37, wherein the bicyclo[x.y.z]alkane, is selected from the group consisting of 2-methylbicyclo[2.1.0]pentane, bicyclo[2.1.1]hexane, 1,4-dimethylbicyclo [2.2.0]hexane, bicyclo[2,2,1]heptane (norbornane), 7,7-dimethylbicyclo[2.2.1]heptane, endo-2-Isopropyl-7,7-dimethylbicyclo[2.2.1]heptane, trans-bicyclo[4.4.0]decan-3-one, bicyclo[2.2.2]octane, 1,4-diisopropylbicyclo[2.2.2]octane, (2S,3S)-2-ethyl-3-methyl-bicyclo[2.2.2]octane, bicyclo[3.1.0]hexane, 2,6,6-Trimethylbicyclo[3.1.1]heptane, bicyclo-[3.2.0]heptane, bicyclo[3.2.2]nonane, bicyclo[3,3,0]octane, 1,2-dimethylbicyclo-[3.3.0]octane, bicyclo[3.3.3]undecane, bicyclo[4.1.0]heptane, (1S,2R,4S,6R)-4-Ethyl-2-isopropylbicyclo[4.1.0]heptane, cis-bicyclo[4.2.1]nonane, 1,9-Dimethylbicyclo-[4.2.1]nonane, trans-1,6-dibromobicyclo[4,3,0]nonane, 1-Methyl-8-propylbicyclo-[4.3.0]nonane, bicyclo[4.3.2]undecane, cis-bicyclo[4.4.0]decane (cis-Decalin), trans-bicyclo[4.4.0]decane (trans-Decalin), and trans-Bicyclo[4.4.0]decan-3-one.
39. The method of claim 34, wherein the turn element is a bridged heterocycle.
40. The method of claim 34, wherein the turn element is a caged polycycle.
41. The method of claim 40, wherein the caged polycycle is selected from the group consisting of adamantane, diamantane, cubane and quadricyclene.
42. The method of claim 34, wherein the turn element is a saccharide.
43. The method of claim 42, wherein the saccharide is a mono-, di- or trisaccharide.
44. The method of claim 42, wherein the saccharide is a pentose or hexose sugar, or pentose or hexose azasugar.
45. The method of any of claims 32-44, wherein at least one turn element provided in the PBM library is a chiral turn element.
46. The method of claim 45, wherein the PBM library includes at least two stereoisomers of a chiral turn element.
47. The method of claim 46, wherein the stereoisomers are enantiomeric chiral turn elements.

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48. The method of claim 46, wherein the stereoisomers are diastereomeric chiral turn elements.
49. The method of any of claims 32-44, wherein the PBM library is variegated with respect to turn elements incorporated in the individual PBMs.
50. The method of claim 42, wherein the PBM library includes MBGs having one or more Lewis basic atoms.
51. The method of claim 50, wherein the Lewis basic atoms are selected from Group 15 and Group 16 atoms.
52. The method of claim 50, wherein the Lewis basic atoms are selected from Nitrogen, Oxygen, Phosphorous and Sulfur.
53. The method of claim 49, wherein the MBGs are selected from the group consisting of amines (primary, secondary, and tertiary), aromatic amines, amino groups, amido groups, nitro groups, nitroso groups, amino alcohols, nitriles, isonitriles, cyanates, isocyanates, imino groups, phosphates, phosphonates, phosphites, substituted and unsubstituted phosphines, phosphine oxides, phosphorothioates, phosphoramidates, phosphonamidites, hydroxyls, carbonyls (e.g., carboxyl, ester and formyl groups), aldehydes, ketones, ethers, carbamoyl groups, thiols, sulfides, thiocarbonyls (e.g., thiolcarboxyl, thiolester and thiolformyl groups), thioethers, mercaptans, sulfonic acids, sulfates, sulfonates, sulfonones, sulfonamides, sulfamoyls and sulfinyls.
54. The method of claim 32, wherein the PBM library is immobilized on an insoluble matrix.
55. The method of claim 32, wherein the metal is a transition metal.
56. The method of claim 32, wherein the metal is a Lanthanide metal.
57. The method of claim 32, wherein the metal is selected from the group consisting of  $\text{Co}^{3+}$ ,  $\text{Cr}^{3+}$ ,  $\text{Hg}^{2+}$ ,  $\text{Pd}^{2+}$ ,  $\text{Pt}^{2+}$ ,  $\text{Pd}^{4+}$ ,  $\text{Pt}^{4+}$ ,  $\text{Rh}^{3+}$ ,  $\text{Ir}^{3+}$ ,  $\text{Ru}^{3+}$ ,  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Fe}^{2+}$ ,  $\text{Au}^{3+}$ ,  $\text{Au}^{+}$ ,  $\text{Ag}^{+}$ ,  $\text{Cu}^{+}$ ,  $\text{MoO}_2^{2+}$ ,  $\text{Ti}^{3+}$ ,  $\text{Bi}^{3+}$ ,  $\text{CH}_3\text{Hg}^{+}$ ,  $\text{Al}^{3+}$ ,  $\text{Ga}^{3+}$ ,  $\text{Ce}^{3+}$ ,  $\text{UO}_2^{2+}$ , and  $\text{La}^{3+}$ .
58. The method of claim 32, wherein the PBM library includes at least  $10^2$  different PBM species.
59. The method of claim 32, wherein the PBM-metal complexes include PBMs which chelate the metal.

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60. The method of claim 32 or 59, wherein the metal of the PBM-metal complexes has at least 2 free coordination sites.
61. The method of claim 32, wherein the ability of the PBM-metal complexes to catalyze a stereoselective reaction is determined.
62. The method of claim 32 or 61, wherein the efficiency of the PBM-metal complexes to catalyze a reaction is determined.
63. The method of claim 32 or 61, wherein the selectivity of the PBM-metal complexes to catalyze a reaction is determined.
64. The method of claim 32, wherein the PBM library includes at least 100 diversomers represented by the general formula:



wherein

A represents a carbocycle or heterocycle which can be monocyclic or polycyclic, aromatic or non-aromatic;

R1 and R2 each represent, independently for each occurrence in a PBM of the PBM library, an MBG including at least one moiety selected from the group consisting of amines (primary, secondary, and tertiary and aromatic amines), amino groups, amido groups, nitro groups, nitroso groups, amino alcohols, nitriles, imino groups, phosphates, phosphonates, phosphites, (substituted) phosphines, phosphine oxides, phosphorothioates, phosphoramidates, phosphonamidites, hydroxyls, carbonyls (e.g., carboxyl, ester and formyl groups), aldehydes, ketones, ethers, carbamoyl groups, thiols, sulfides, thiocarbonyls (e.g., thiolcarboxyl, thiolester and thiolformyl groups), thioethers, mercaptans, sulfonic acids, sulfates, sulfonates, sulfonones, sulfonamides, sulfamoyls and sulfinyls, or alkyl, alkenyl or alkynyl groups (preferably in the range of C<sub>1</sub>-C<sub>30</sub>) substituted therewith;

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R3 is absent or represents one or more further MBG substitutions to the ring A, each occurrence of which independently includes a moiety selected from the group consisting of amines (primary, secondary, and tertiary and aromatic amines), amino groups, amido groups, nitro groups, nitroso groups, amino alcohols, nitriles, imino groups, phosphates, phosphonates, phosphites, (substituted) phosphines, phosphine oxides, phosphorothioates, phosphoramidates, phosphonamidites, hydroxyls, carbonyls (e.g., carboxyl, ester and formyl groups), aldehydes, ketones, ethers, carbamoyl groups, thiols, sulfides, thiocarbonyls (e.g., thiolcarboxyl, thiolester and thiolformyl groups), thioethers, mercaptans, sulfonic acids, sulfates, sulfonates, sulfonones, sulfonamides, sulfamoyls and sulfinyls, or alkyl, alkenyl or alkynyl groups (preferably in the range of C<sub>1</sub>-C<sub>30</sub>) substituted therewith

- (b) isolating PBMs from the PBM library on the basis of ability to bind to a metal or ion.
- 
- 65. A library of potential metal binding ligands comprising at least one turn element represented by the general formula: T-R1(-R2)(-R3), wherein T is a turn element, R1 and R2 are, individually, substituents of turn element T each having at least one Lewis basic moiety for binding to a metal atom, and R3 is absent or represents one or more substituents of T each having at least one Lewis basic moiety for binding to a metal atom.
  - 66. A library of potential organo-metallic catalysts comprising at least one turn element represented by the general formula: T-R1(-R2)(-R3), wherein T is a turn element, R1 and R2 are, individually, substituents of turn element T each having at least one Lewis basic moiety for binding to a metal atom, and R3 is absent or represents one or more substituents of T each having at least one Lewis basic moiety for binding to a metal atom.
  - 67. A chelating agent identified according to the method of any of claims 1-30.
  - 68. An organo-metallic catalysts identified according to the method of any of claims 32-64.

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69. The method of claim 24, wherein the metal-PBM complexes are further selected on the basis of their ability to catalyze a metal-catalyzed reaction.
70. The method of claim 25, wherein the metal-PBM complexes are further selected on the basis of their ability to catalyze a transition metal-catalyzed reaction.
71. The method of claim 26, wherein the metal-PBM complexes are further selected on the basis of their ability to catalyze a lanthanide-catalyzed reaction.
72. The method of claim 69-71, wherein the catalyzed reaction is stereoselective.
73. The method of claim 32, wherein the reaction is a ring-opening, a carbonyl addition, a carbonyl reduction, an olefin addition, an olefin reduction, an imine addition, an imine reduction, a cycloaddition, a sigmatropic rearrangement, an olefin epoxidation, or an olefin aziridination.
74. The method of claim 32, wherein the metal-PBM complexes are identified on the basis of their ability to catalyze a reaction which results in a change in absorbance of light of any wavelength, the evolution of gas, a temperature change, or any combination of these results.

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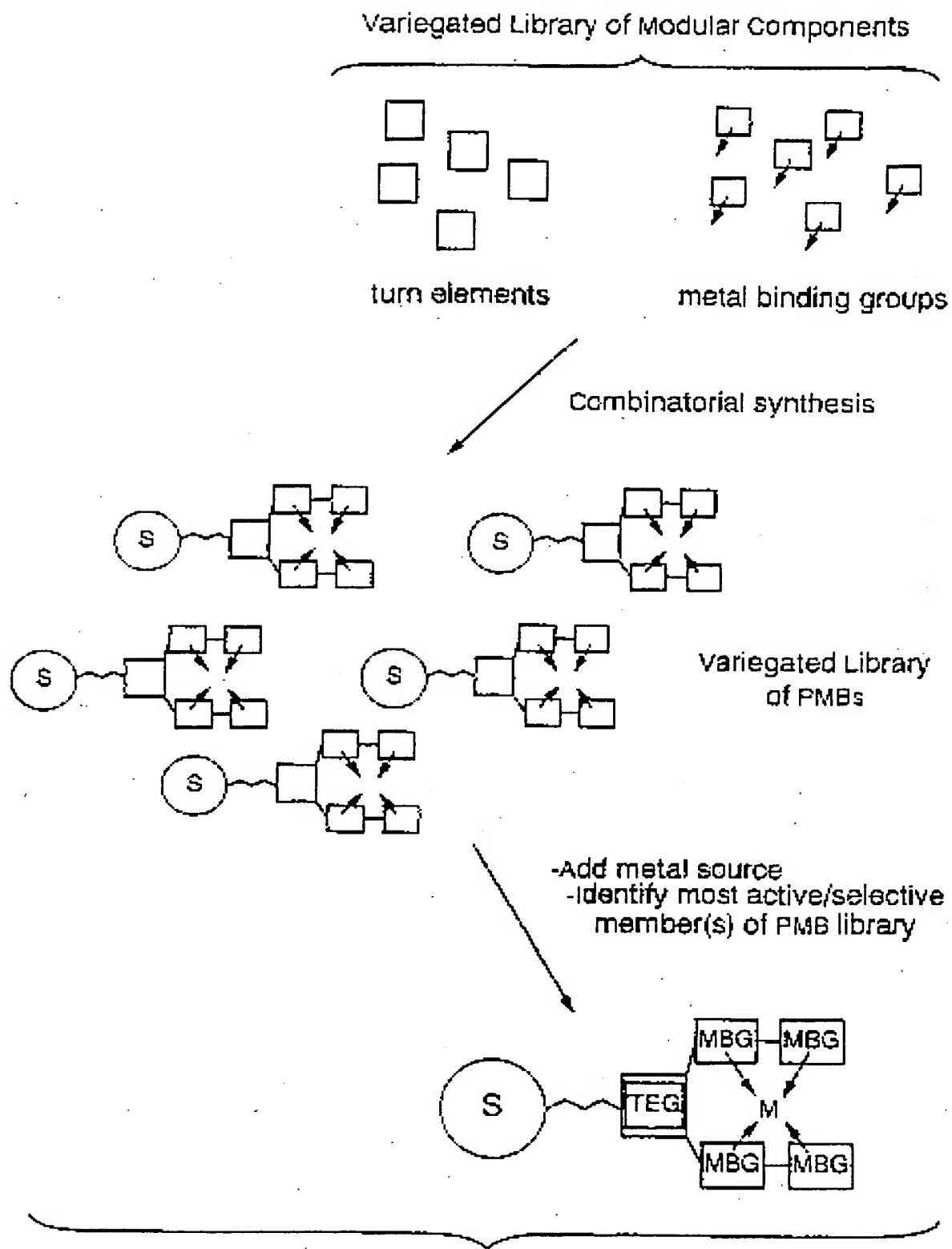
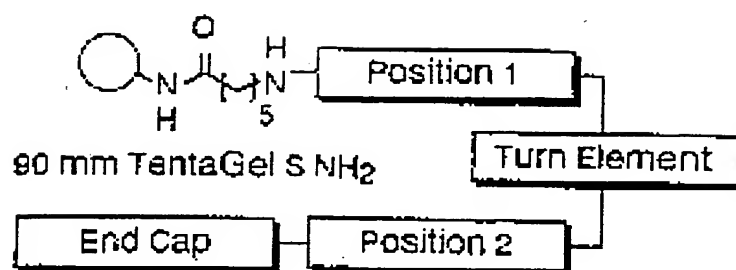


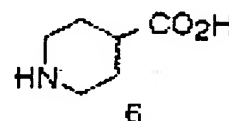
FIG. 1

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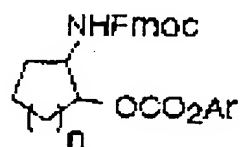


Position 1:  
 L- or O-Asp(OtBu)  
 L- or O-Ser(OtBu)  
 L- or O-Met  
 L- or O-Tyr(OtBu)  
 L- or O-Phg  
 L- His(Trt)  
 Gly

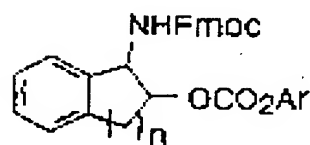
Position 2:  
 L-Asp(OtBu) L-Phg  
 L-Ser(OtBu) Gly  
 L-Tyr(OtBu)  
 L- His(Trt)  
 L-Met  
 L-Trp



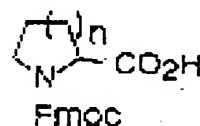
Turn Element Monomers: (Ar=p-nitrophenyl)



1a: (1S,2S), n=1  
 1b: (1R,2R), n=1  
 2a: (1S,2S), n=2  
 2b: (1R,2R), n=2

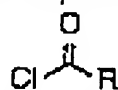


3a: (1S,2R), n=1  
 3b: (1R,2S), n=1  
 4a: (1S,2R), n=2  
 4b: (1R,2S), n=2



5a: (2S), n=1  
 5b: (2R), n=2

End Cap Monomers:



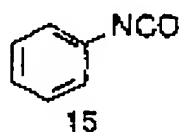
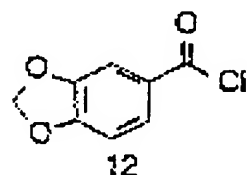
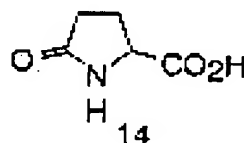
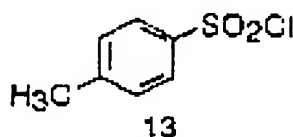
7: R = CH<sub>3</sub>

8: R = tBu

9: R = 1-Naphthyl

10: R = CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>

11: R = 2-Pyridyl



<Blank>

FIG. 2A

SUBSTITUTE SHEET (RULE 26)

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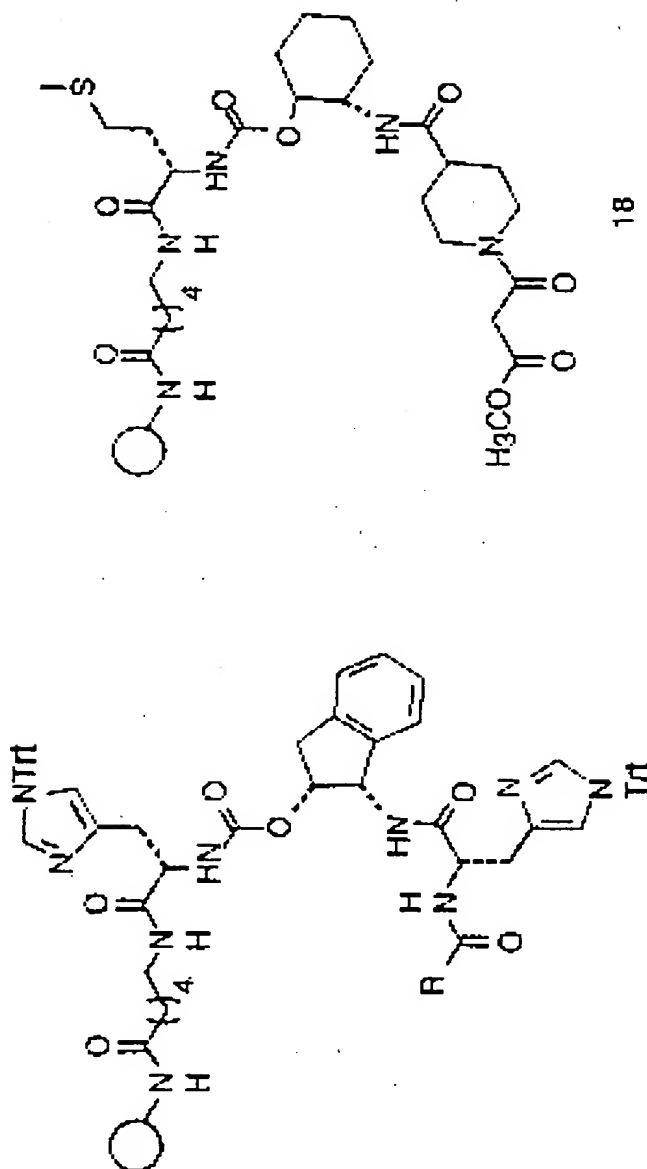
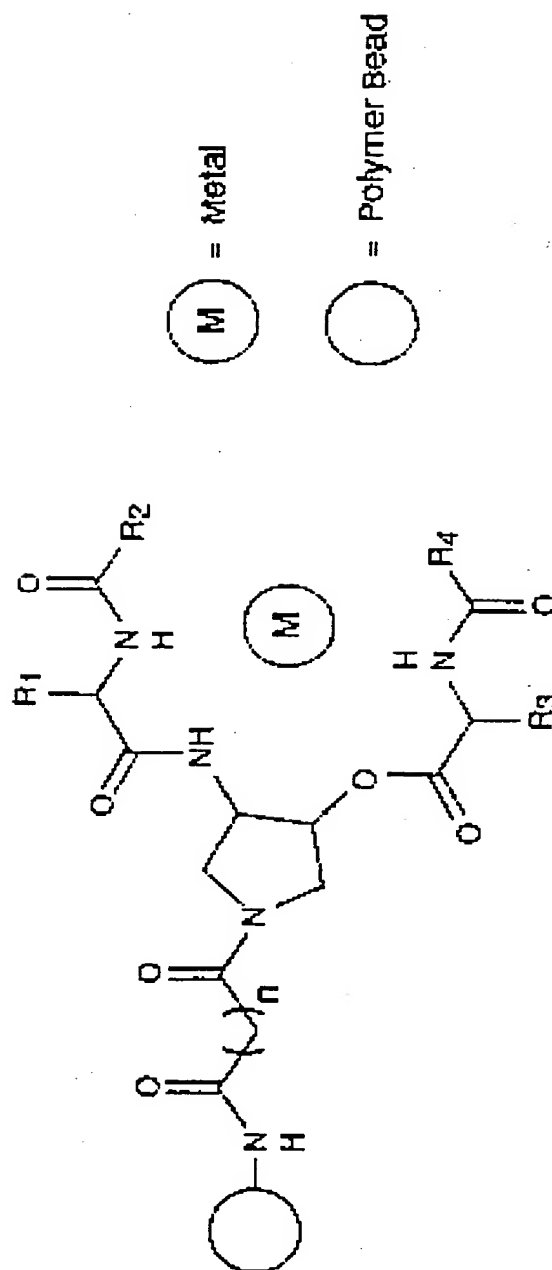


FIG. 2B

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- Amino acids provide structural and functional group diversity
- Turn element induces interactions between peptide chains
- Commercially available acylating reagents increase diversity
- Ligands encoded by established methods  
(W.C. Still et al. PNAS. 1993, 90, 10922).

FIG. 3A

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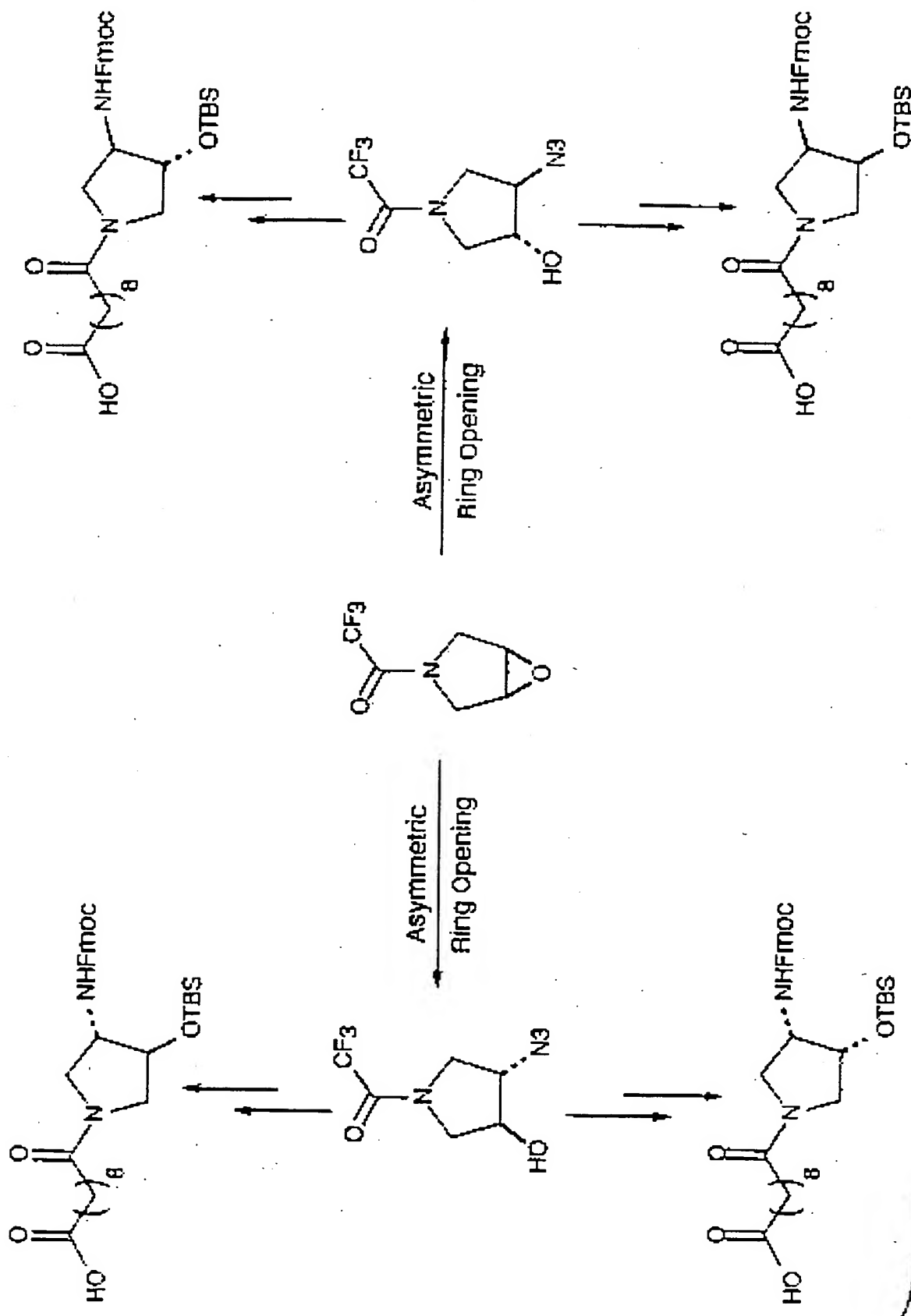
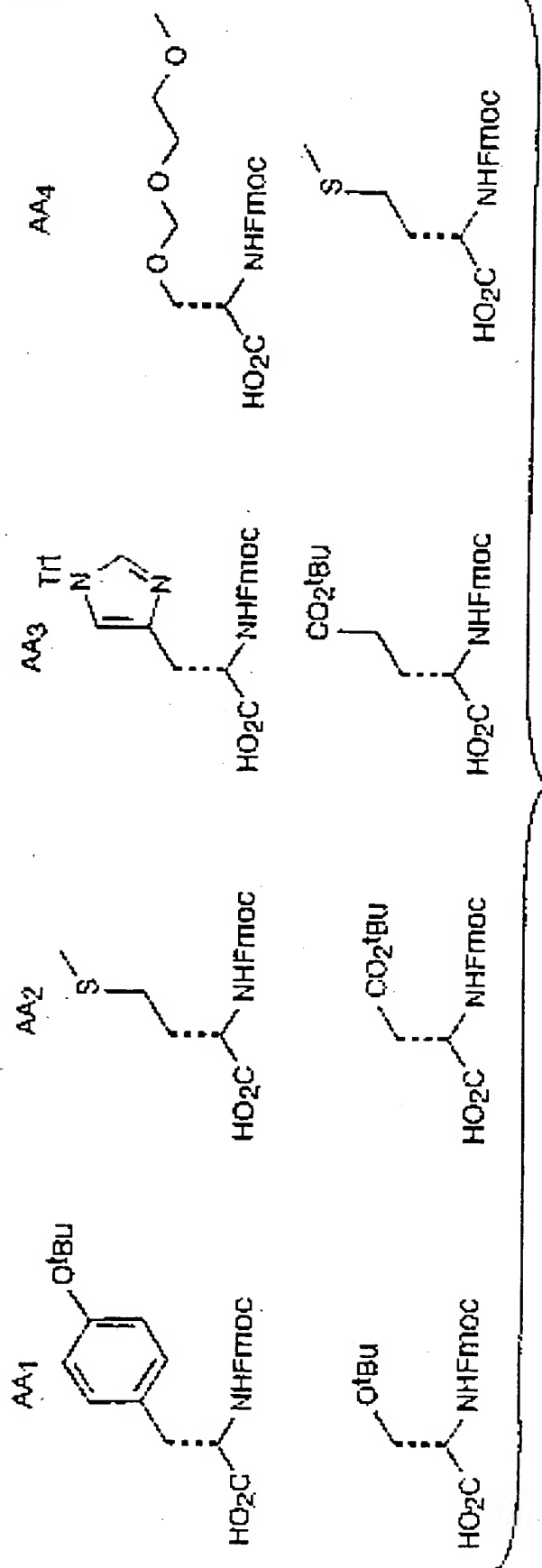
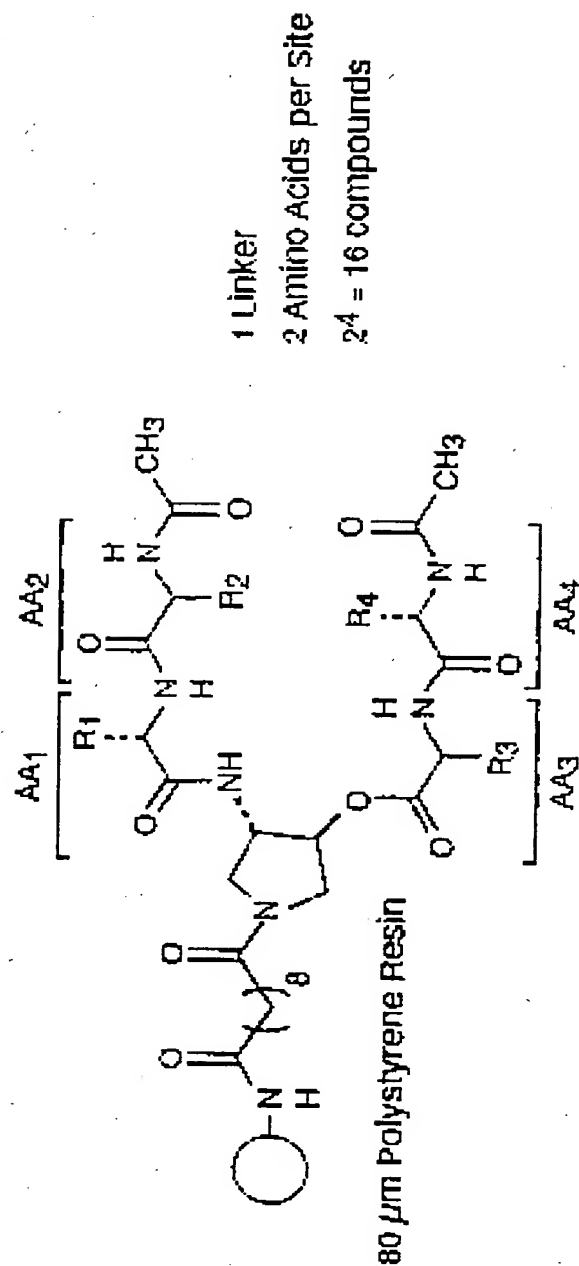


FIG. 3B

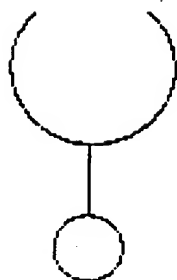


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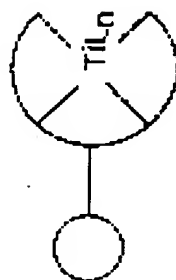
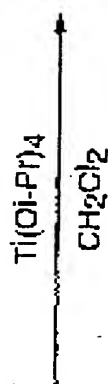


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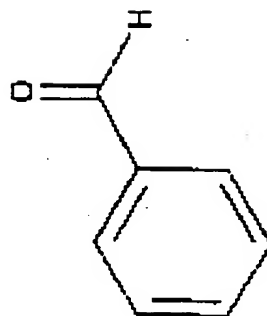
+



Ligand Library

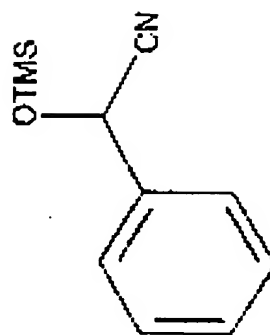


Metal-Ligand Library



2 eq. TMSCN

Metal-Ligand Library

CH<sub>2</sub>Cl<sub>2</sub>, 2 hours

Vial	eq. Ligand	eq. Ti(Oi-Pr) <sub>4</sub>	Rel. Conversion	% ee
1	0.1	0.1	59%	8%
2	0	0.1	<1%	---
3	0.1	0	51%	11%

FIG. 4B

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2 Linker  
10 Amino Acids  
2 x 10<sup>2</sup> = 200 compounds

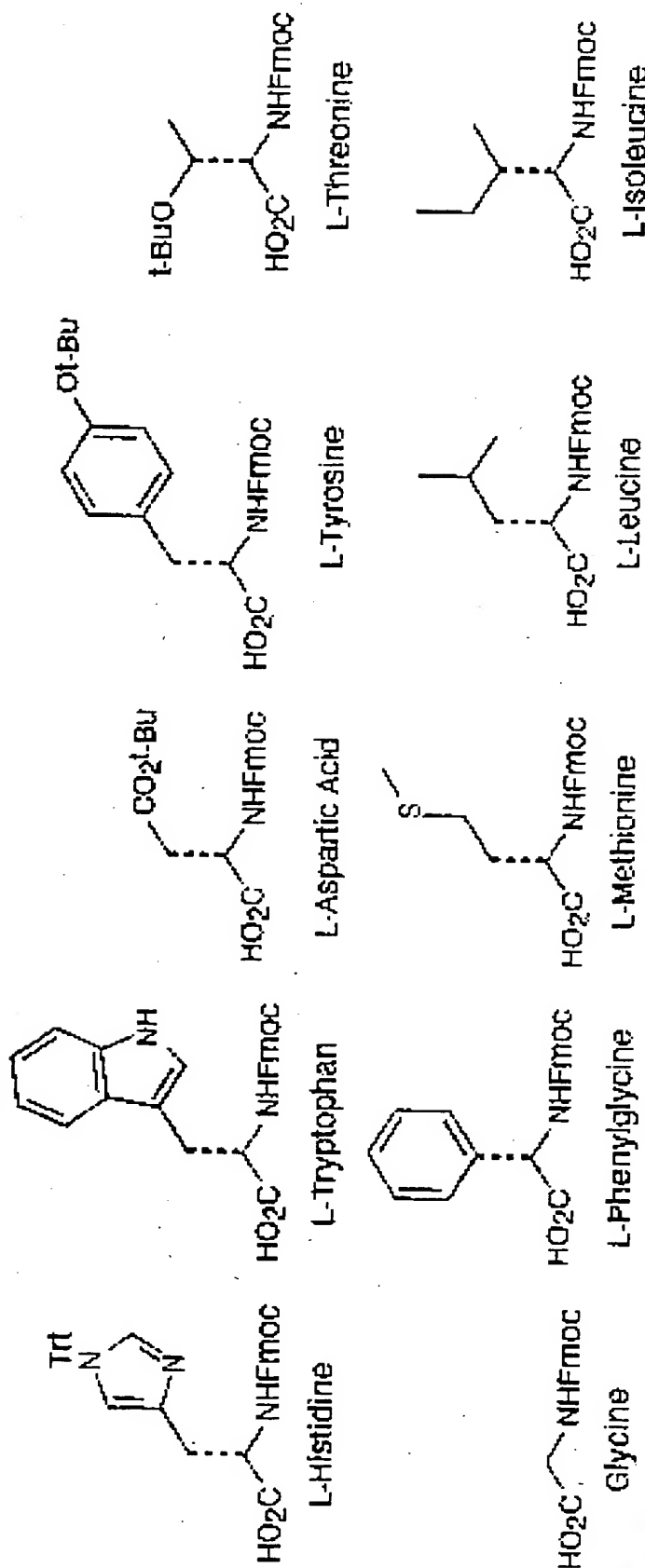
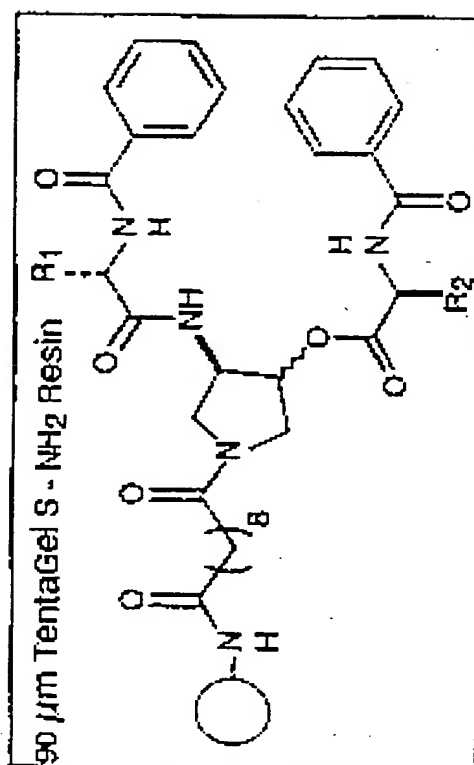


FIG. 4C

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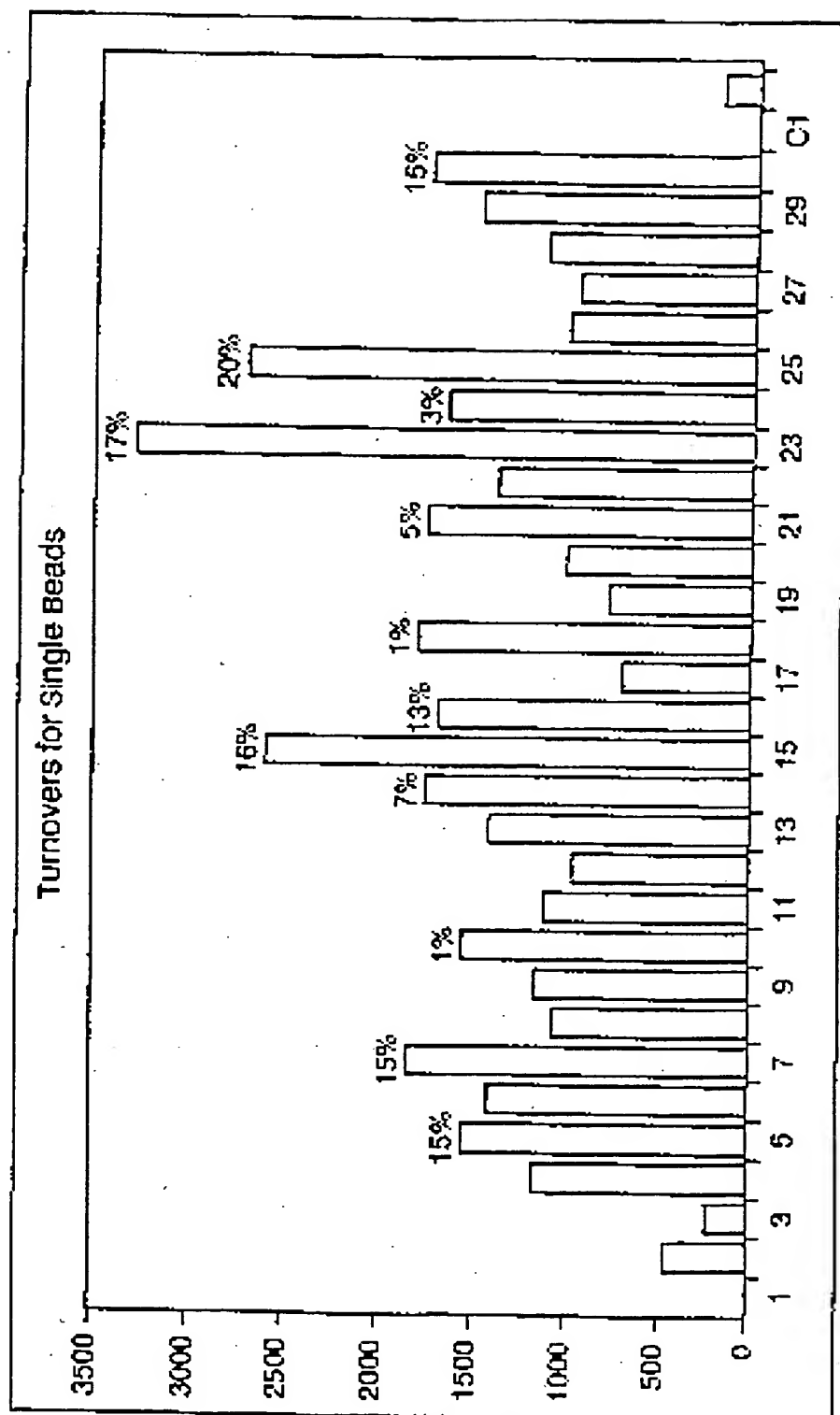
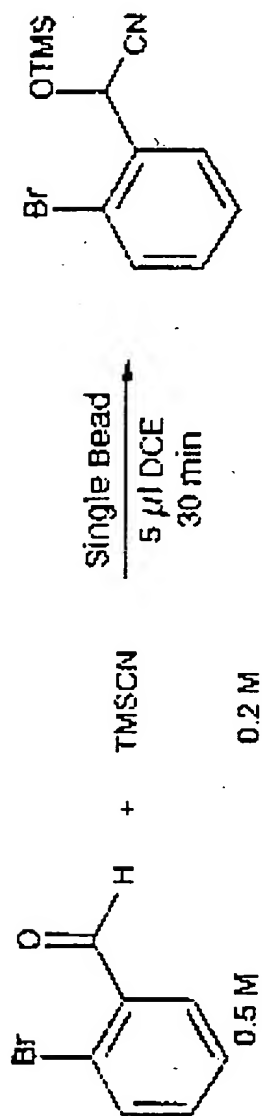


FIG. 4D

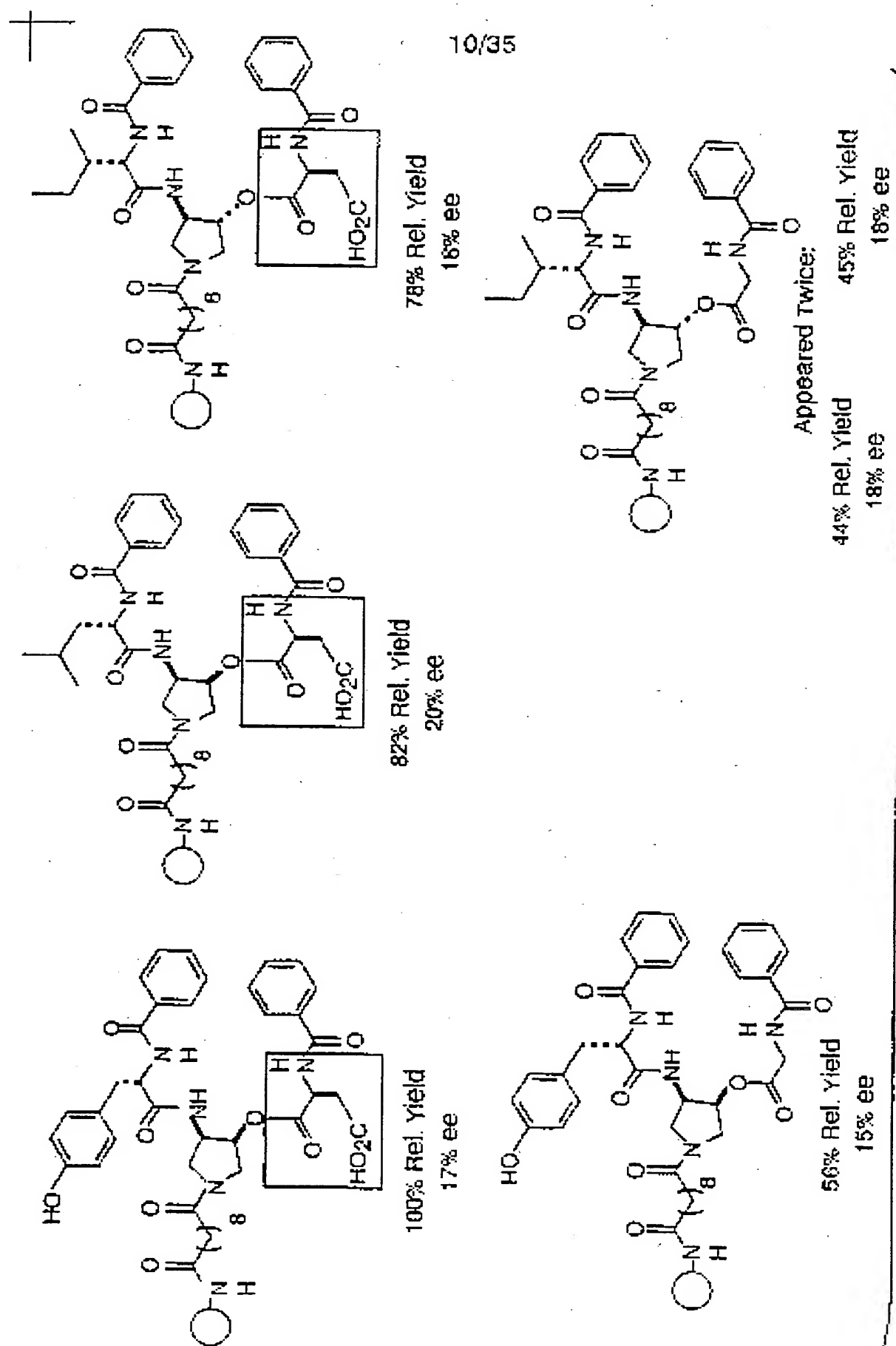


FIG. 4E

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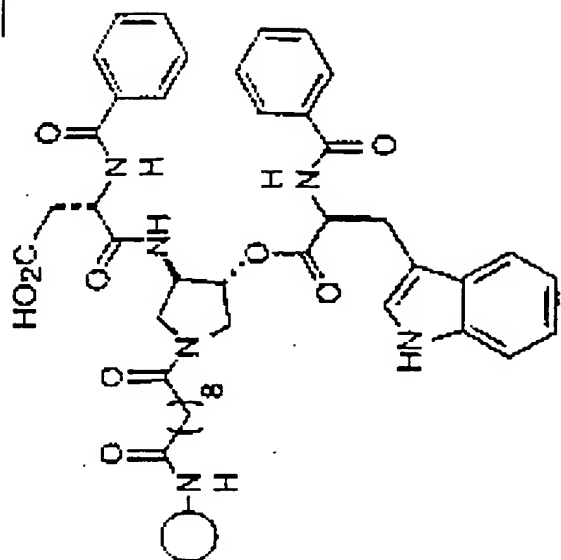
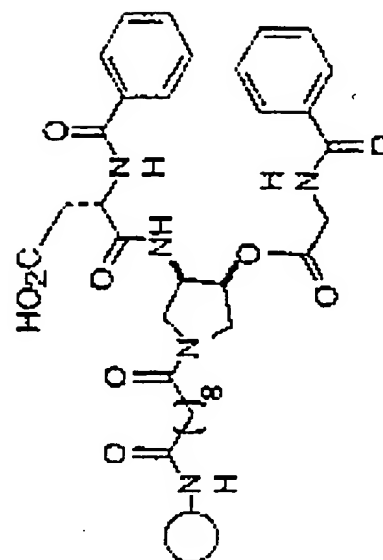
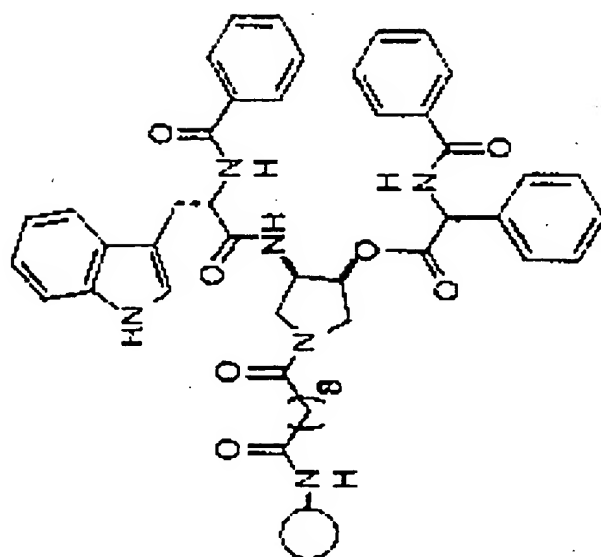
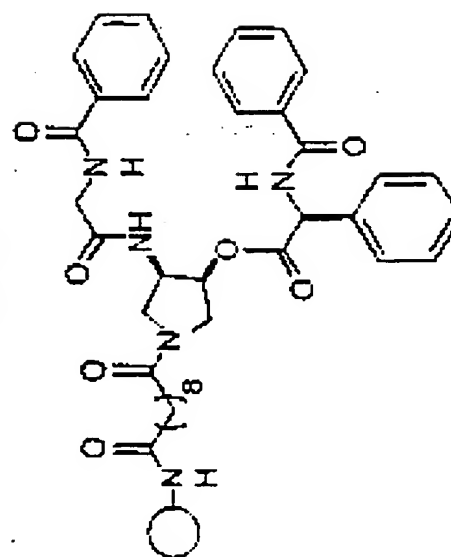
41% Rel. Yield  
6% ee23% Rel. Yield  
% ee Not Measured53% Rel. Yield  
15% ee48% Rel. Yield  
1% ee

FIG. 4F

SUBSTITUTE SHEET (RULE 26)

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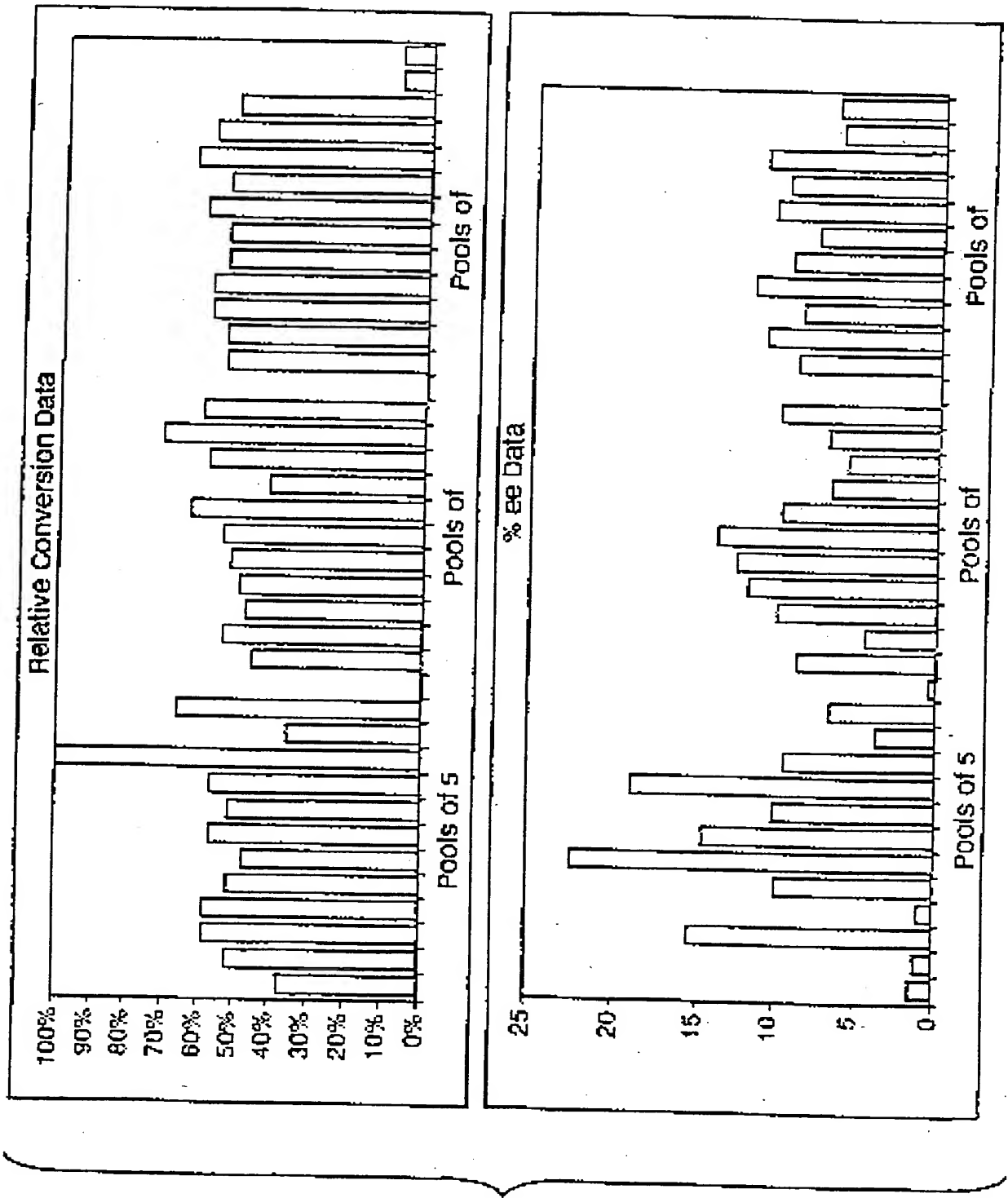


FIG. 4G



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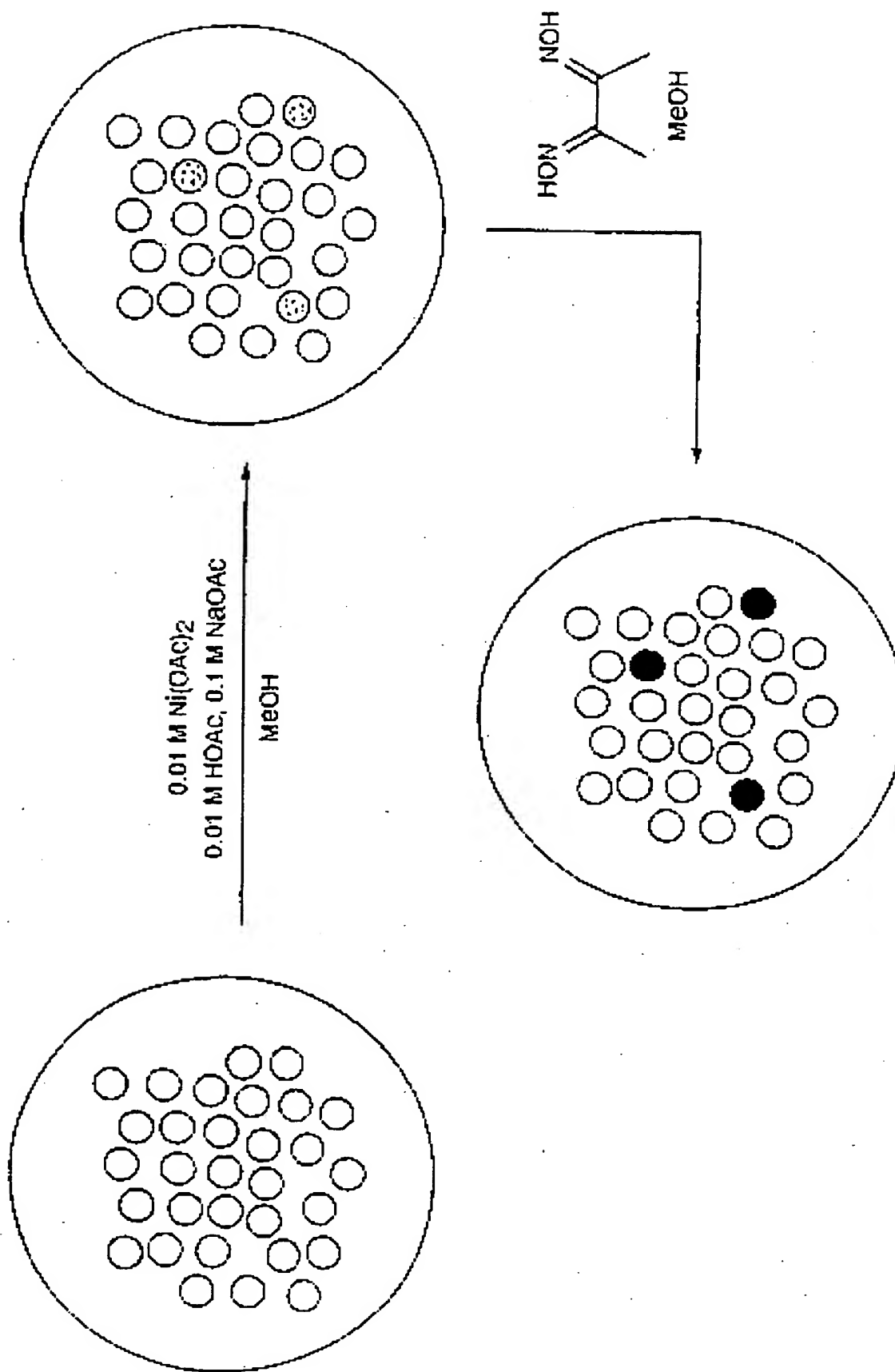


FIG. 5A

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Structure	Linker	Amino Acid 1	End Cap 1	Amino Acid 2	End Cap 2
1	(R,S)-cis	His(Trt)	Bz	Pho	Bz
2	(R,S)-cis	His(Trt)	Bz	Trp	Bz
3	(R,S)-cis	His(Trt)	Bz	Pho	Bz
4	(R,S)-cis	His(Trt)	Bz	Pho	Bz
5	(R,S)-cis	His(Trt)	Bz	Thr(tBu)	Bz
6	(R,R)-trans	His(Trt)	Bz	Gly	Bz
7	(R,S)-cis	His(Trt)	Bz	Pho	Bz
8	(R,R)-trans	His(Trt)	Bz	Ile	Bz
9	(R,S)-cis	His(Trt)	Bz	Thr(tBu)	Bz
10	(R,R)-trans	His(Trt)	Bz	Asp(tBu)	Bz
11	(R,R)-trans	His(Trt)	Bz	Gly	Bz
12	(R,S)-cis	His(Trt)	Bz	His(Trt)	Bz

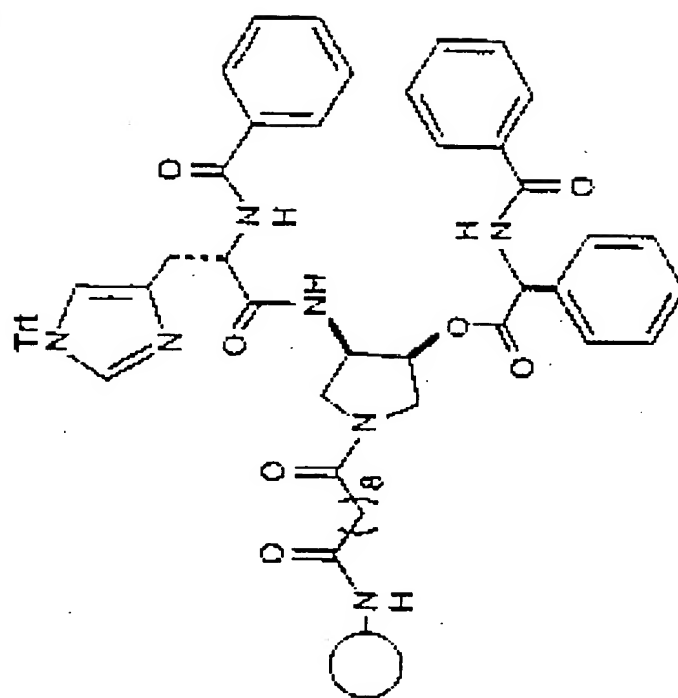


FIG. 5B

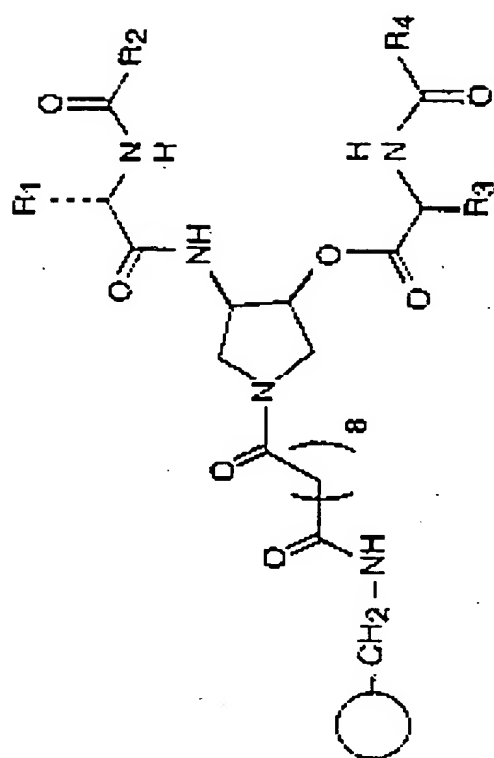
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4 diastereomeric linkers

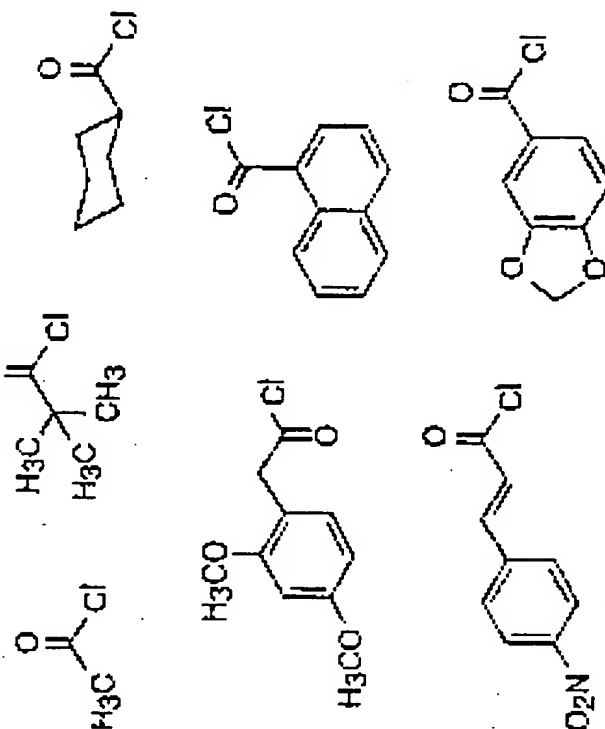
7 amino acids

7 acyl caps

72 x 72 x 4 = 9604 Ligands



Acyl Caps



Amino Acids

L-His

L-Tyr

L-Leu

L-Trp

L-Asp

L-Thr

Gly

FIG. 5C

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Structure	Linker	Amino Acid 1	End Cap 1	Amino Acid 2	End Cap 2
1	?	His(Trt)	Piv	Asp(tBu)	Pip
2	?	His(Trt)?	Piv	Leu	Piv
3	(R,S)-cis	His(Trt)	Piv	Asp(tBu)	Dmb
4	(S,R)-cis	His(Trt)	Piv	His(Trt)	Pip
5	(S,R)-cis	His(Trt)	Pip	Tyr(tBu)	Dmb
6	?	His(Trt)?	Cln	Asp(tBu)	Acv
7	cis	His(Trt)	Cln	Gly	Acv
8	(S,R)-cis	His(Trt)	Dmb	Thr(tBu)	Dmb
9	?	His(Trt)	Piv	Asp(tBu)	Acv
10	(S,R)-cis	His(Trt)	Piv	Asp(tBu)	Nap
11	cis	His(Trt)	Cln	Thr(tBu)	Pip
12	?	Tyr(tBu)	Dmb	His(Trt)	Cyc

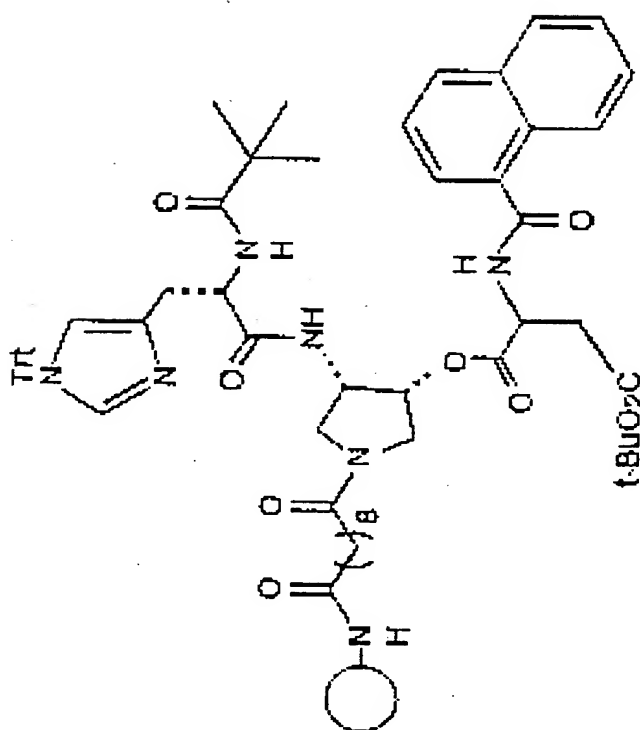
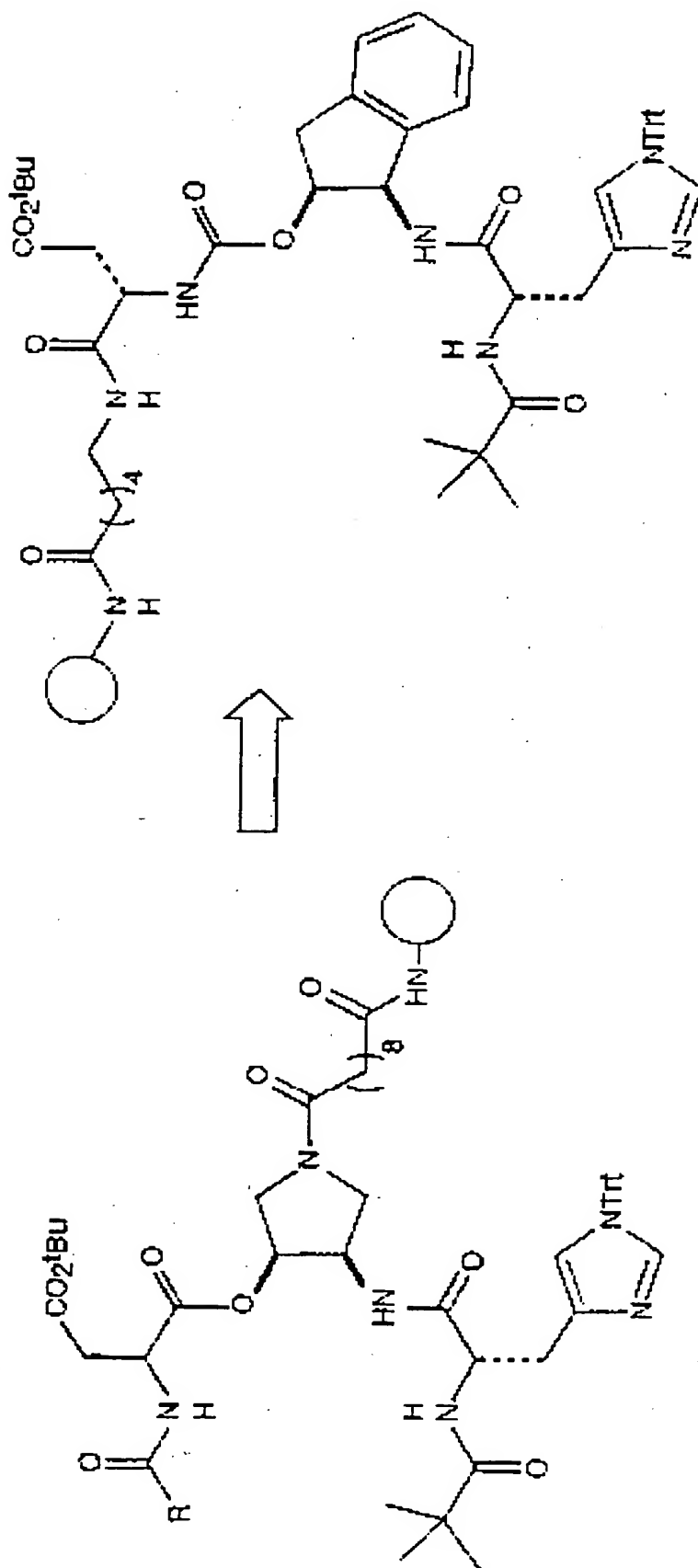


FIG. 5D

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- Maintains Key Structural Elements
- Allows Turn Element Diversity
- Easier to Synthesize

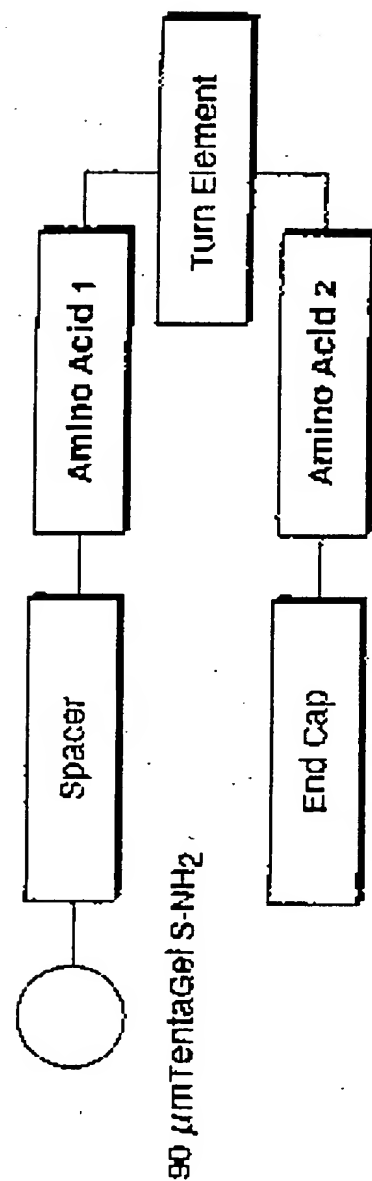
- Identified  $Ni^{2+}$  Binder

FIG. 6

SUBSTITUTE SHEET (RULE 26)



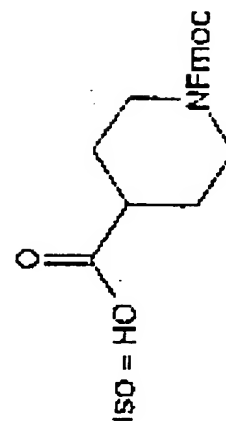
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Coupling Conditions: 5 eq Fmoc-Amino Acid, 5 eq HBTU,  
5 eq HOBT, 10 eq DIPEA, DMF, 2h

FIG. 7B

Position 1		Position 2	
D/L-Asp	D/L-Phg	L-Asp	L-Phg
Gly	D/L-Ser	Gly	L-Ser
L-His	D/L-Tyr	L-His	L-Tyr
D/L-Met		ISO	L-Trp
		L-Met	<Blank>



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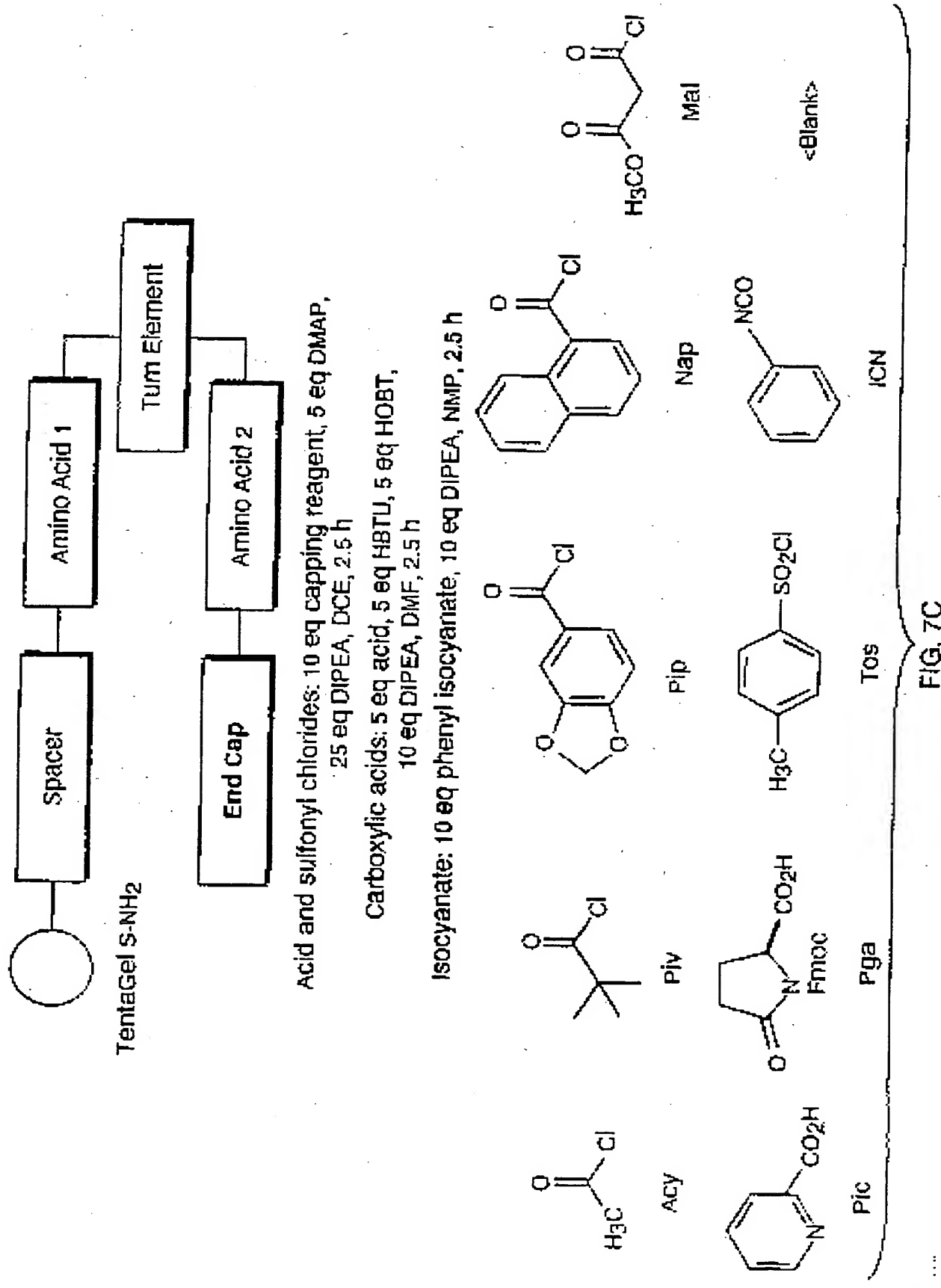
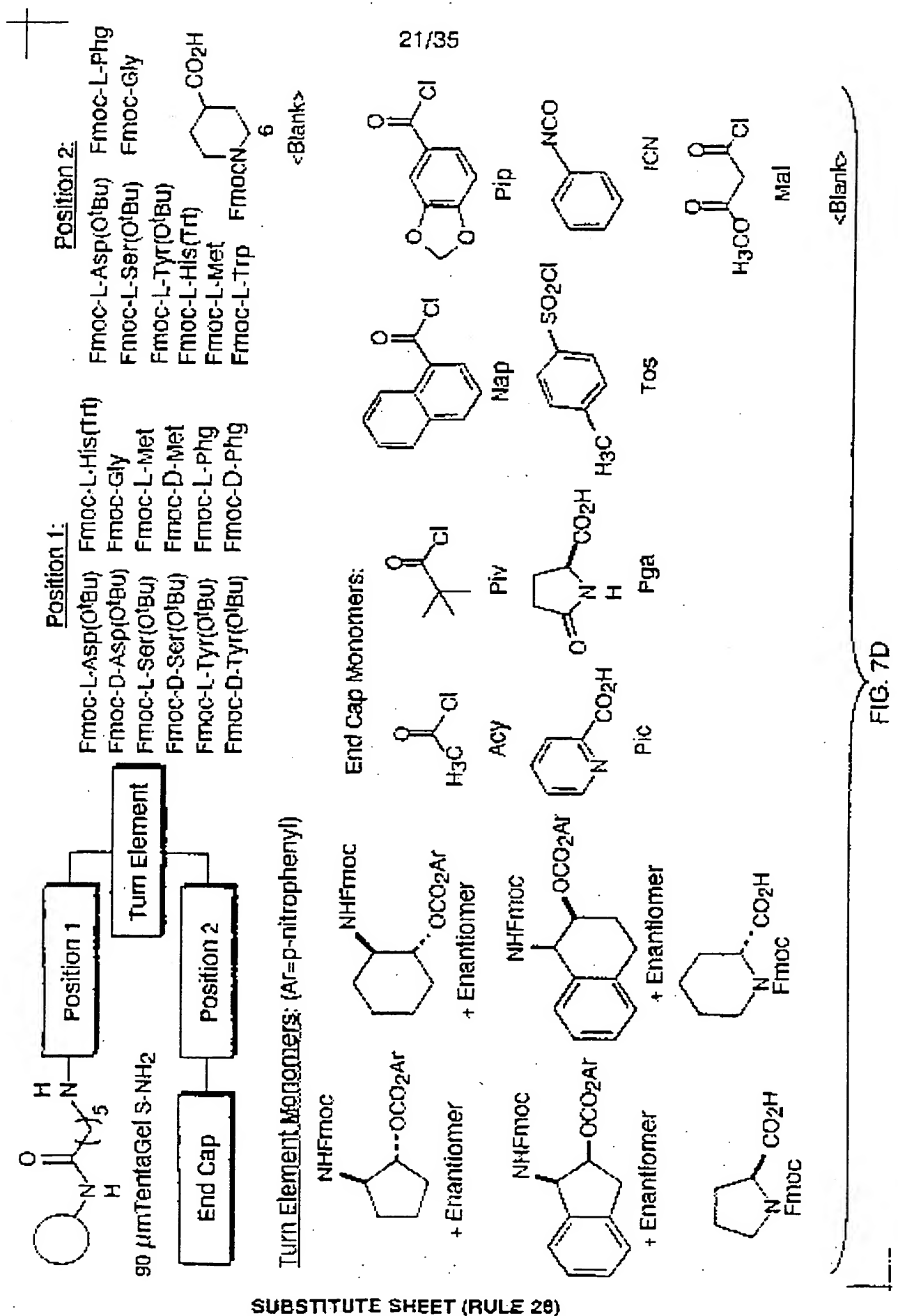


FIG. 7C



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Structure	Position 1	Turn Element	Position 2	End Cap
1	L-His(Trt)	(R,S)-Ind	L-His(Trt)	Pic
2	L-His(Trt)	(S,R)-Ind	L-His(Trt)	Pga
3	L-His(Trt)	(S,R)-Ind	L-His(Trt)	Acy
4	L-His(Trt)	(R,S)-Ind	L-Met	Pip
5	L-His(Trt)	(S,R)-Nap	L-Met	Pip
6	L-His(Trt)	(S,R)-Nap	L-Met	Tos
7	L-His(Trt)	(R,R)-Cyp	L-Phg	<Blank>
8	L-His(Trt)	(R,R)-Cyp	L-Phg	Pic
9	L-His(Trt)	(R,R)-Cyp	L-His(Trt)	Pic
10	L-His(Trt)	(R,R)-Cyp	L-Asp(tBu)	Ich
11	L-His(Trt)	D-Pip	Gly	Ich
12	Gly	(S,S)-Chx	L-His(Trt)	Nap

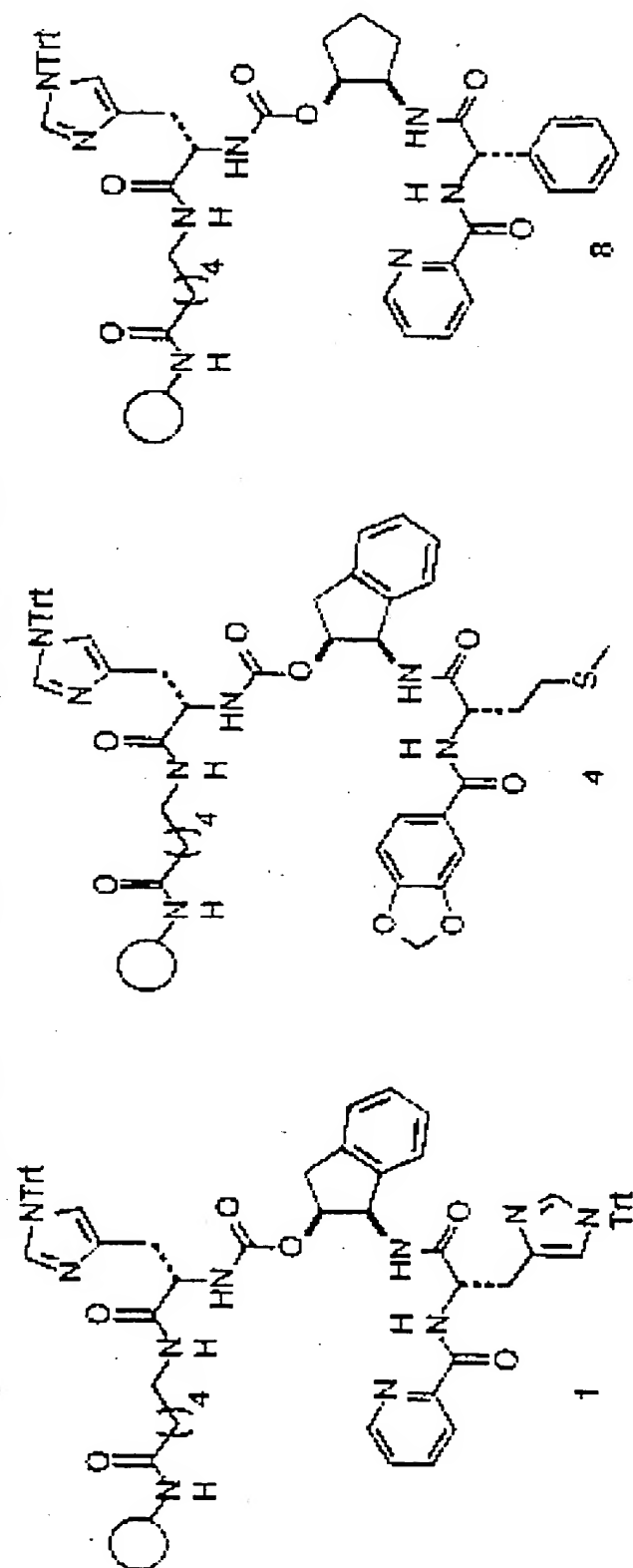


FIG. 7E

SUBSTITUTE SHEET (RULE 26)

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Protected Library IV

1.  $2.5 \times 10^{-4}$  M Ni(OAc)<sub>2</sub>  
in buffered MeOH, 12 h

2. MeOH Rinse and DMG stain

Binders were sequenced

Structure	Amino Acid 1	Turn Element	Amino Acid 2	End Cap
1	L-His(Trt)	(S,R)-Ind	L-His(Trt)	Acv
2	L-His(Trt)	(S,R)-Ind	L-His(Trt)	Acv
3	L-His(Trt)	(S,R)-Ind	L-His(Trt)	Nap
4	L-His(Trt)	(S,R)-Ind	L-His(Trt)	Nap
5	L-His(Trt)	(S,S)-Chx	L-His(Trt)	Acv
6	L-His(Trt)	(S,S)-Chx	L-His(Trt)	Nap

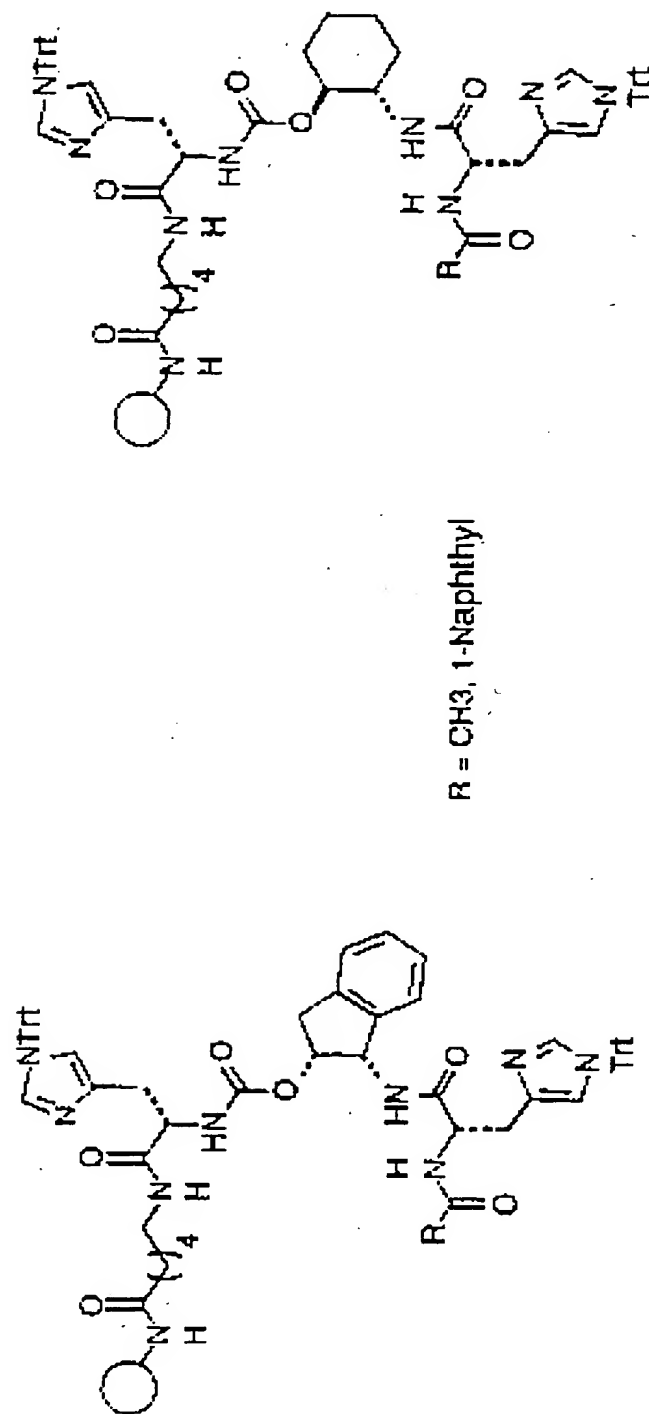
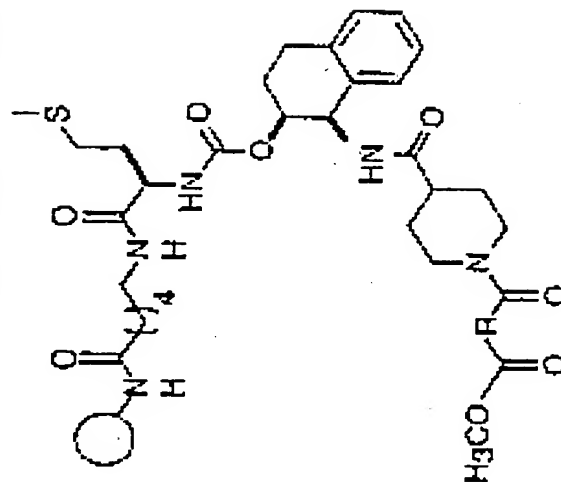


FIG. 8

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Structure	Amino Acid 1	Turn Element	Amino Acid 2	End Cap
1	D-Asp(OBu)	(R,S)-Nap	Iso	Mal
2	D-Ser(OBu)	(R,S)-Ind	Iso	Mal
3	D-Ser(OBu)	(S,R)-Ind	Iso	Mal
4	L-Tyr(OBu)	(R,R)-Chx	Iso	Mal
5	L-Tyr(OBu)	(S,R)-Nap	Iso	Mal
6	D-Tyr(OBu)	D-Pip	Iso	Mal
7	Gly	(R,R)-Cyp	Iso	Mal
8	L-Met	D-Pip	Iso	Mal
9	L-Met	D-Pip	Iso	Mal
10	L-Met	(R,S)-Nap	Iso	Mal
11	D-Met	(R,S)-Nap	Iso	Mal
12	D-Met	(R,S)-Nap	Iso	Mal
13	D-Met	(S,R)-Ind	Iso	Mal
14	D-Met	(S,S)-Cyp	Iso	Mal

FIG. 9



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Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge
Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn
Ln	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb

 = Successfully Bound  
 = Not Incorporated  
 = Not Yet Tried

Cu<sup>2+</sup>: Binds to 30% of the library  
 Prefers His-His Structures

Pd<sup>2+</sup>: Binds to 90% of the library

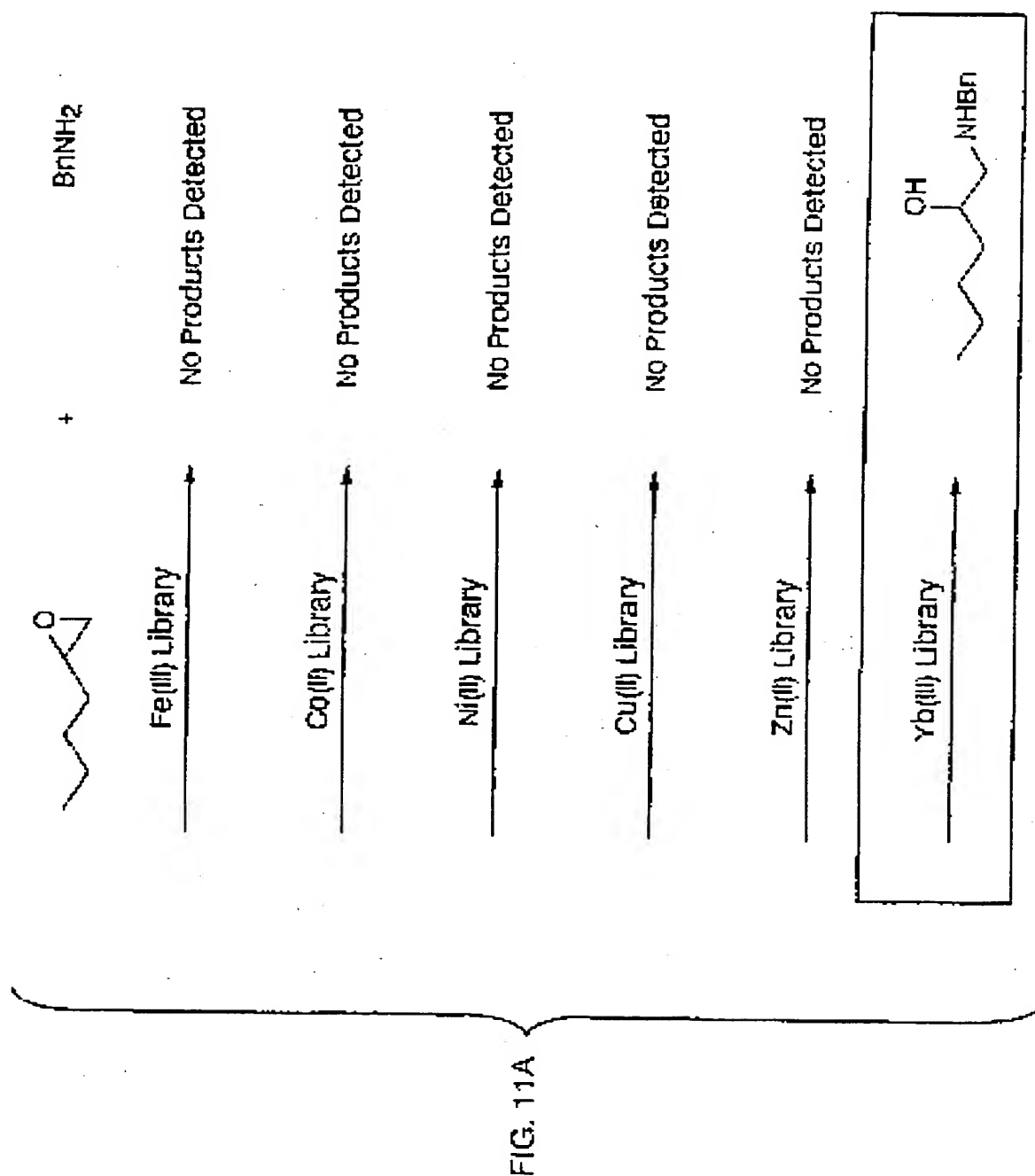
Pt<sup>4+</sup>: Binds to 20% with a Met preference in Pos. 1

Sn<sup>4+</sup>: Binds weakly to 50%, and more strongly to 10%

Ce, Yo

FIG. 10

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Structure	Position 1	Turn Element	Position 2	End Cap
1	D-His	L-Leu	D-His	Fur
2	L-His	L-Leu	D-His	Fur
3	D-His	L-Leu	D-His	Nap
4	L-His	(S,S)-Cyp	L-His	Fur
5	L-His	(S,S)-Cyp	D-His	Nap
6	D-His	Eth	L-His	Acy
7	D-Met	L-Leu	D-His	Nap
8	L-Met	L-Leu	L-His	Pip
9	D-Met	L-Leu	D-His	Pip
10	L-Met	D-Phg	L-His	Fur
11	L-Met	D-Phg	L-His	Acy
12	L-His	(S,R)-Ind	D-Met	Acy

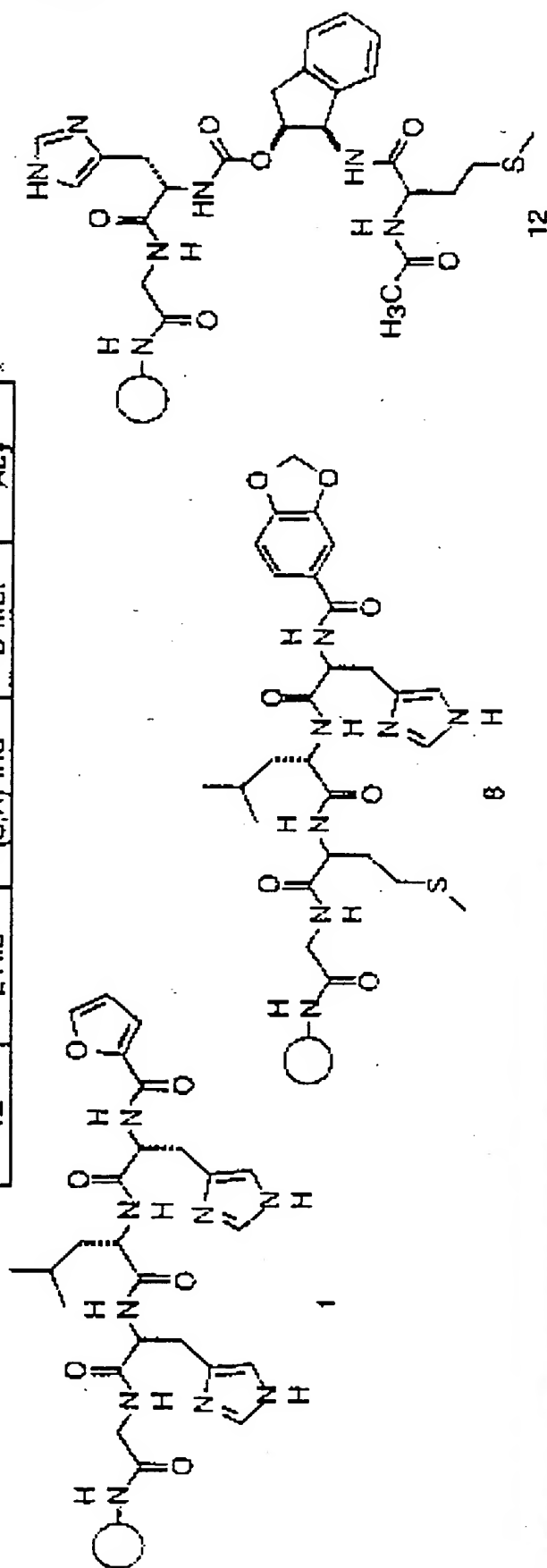


FIG. 11B

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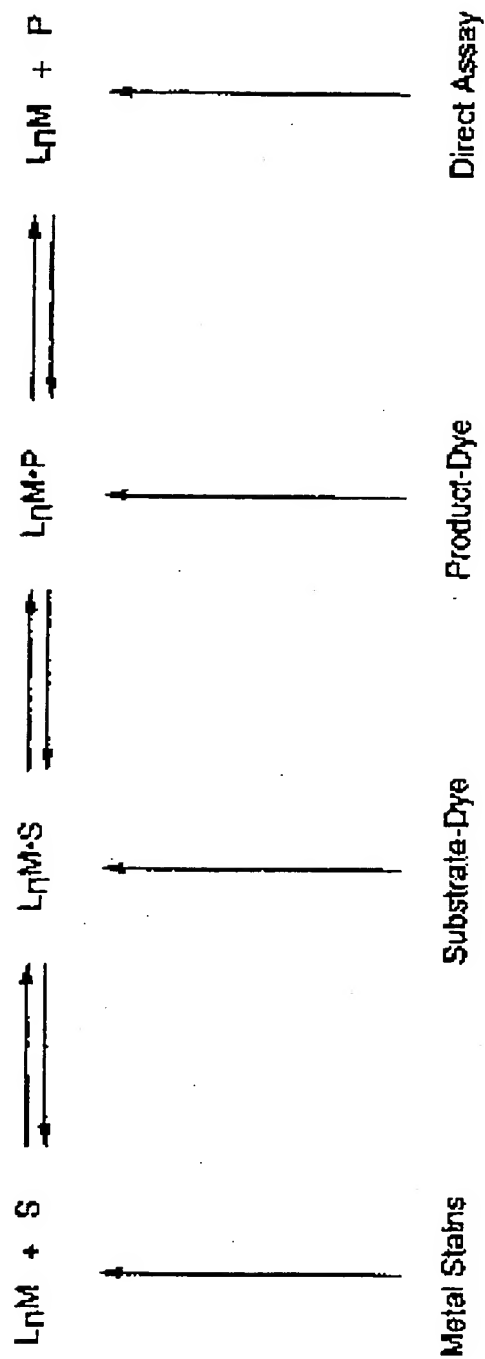
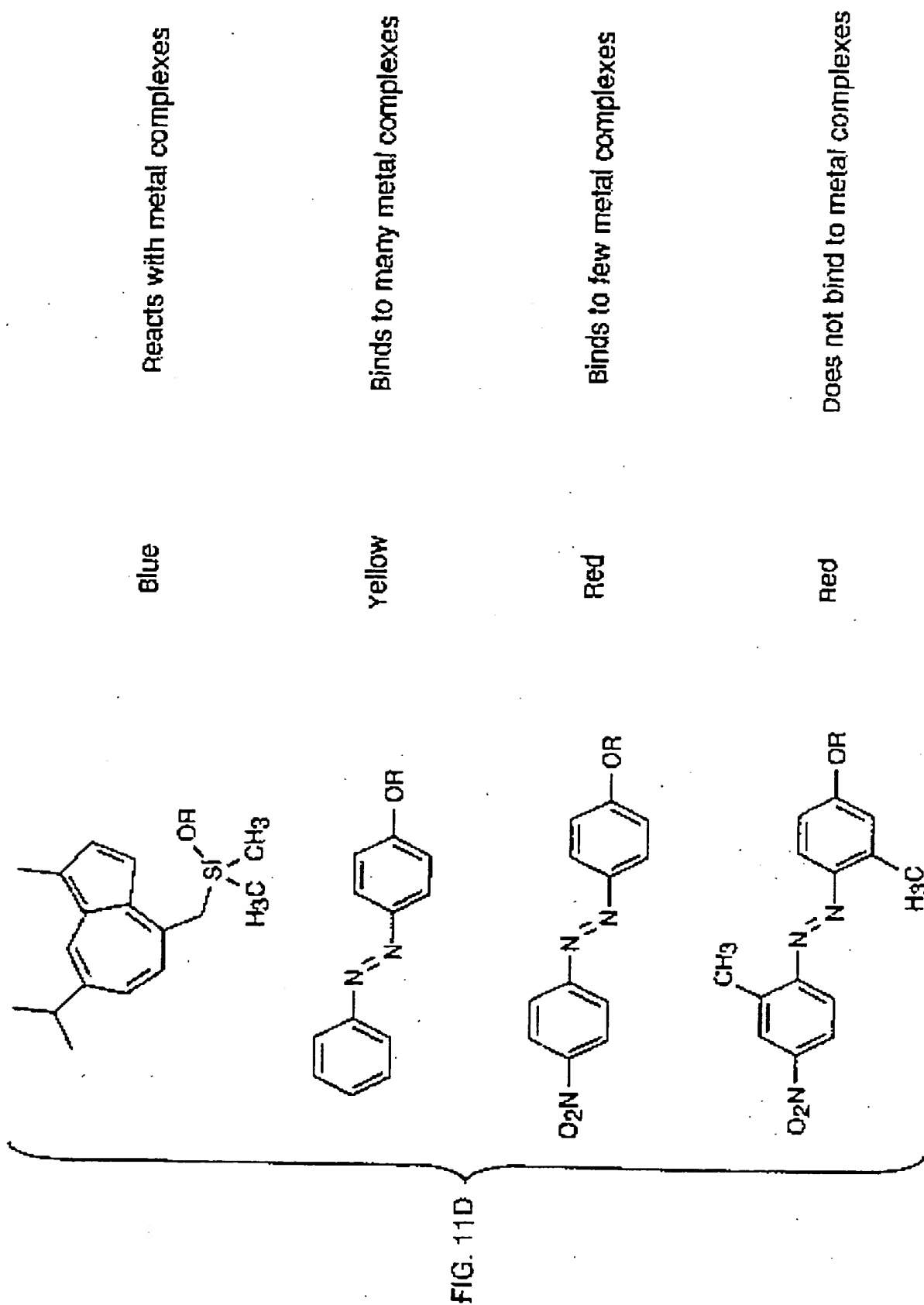


FIG. 11C

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SUBSTITUTE SHEET (RULE 26)

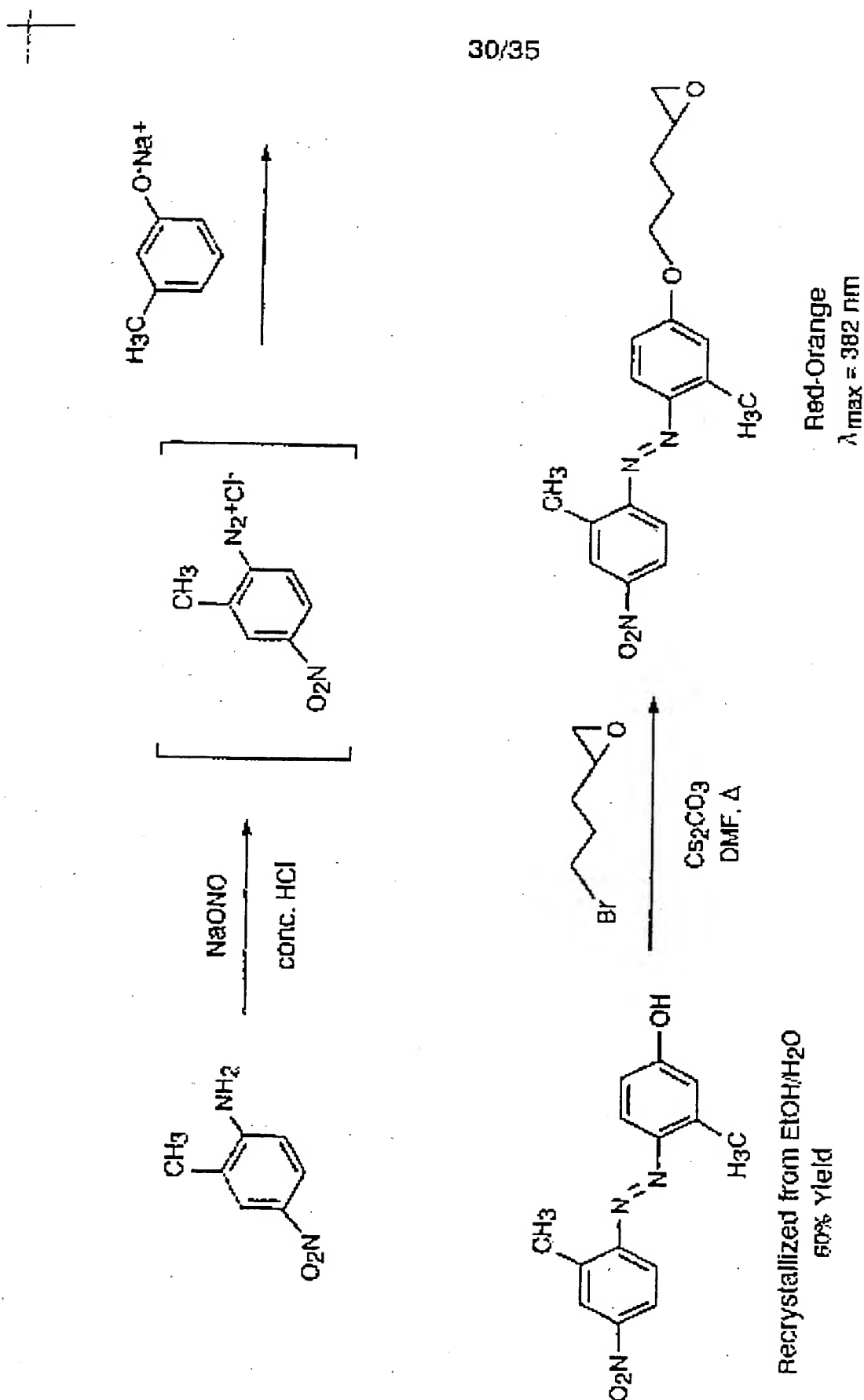


FIG. 11E

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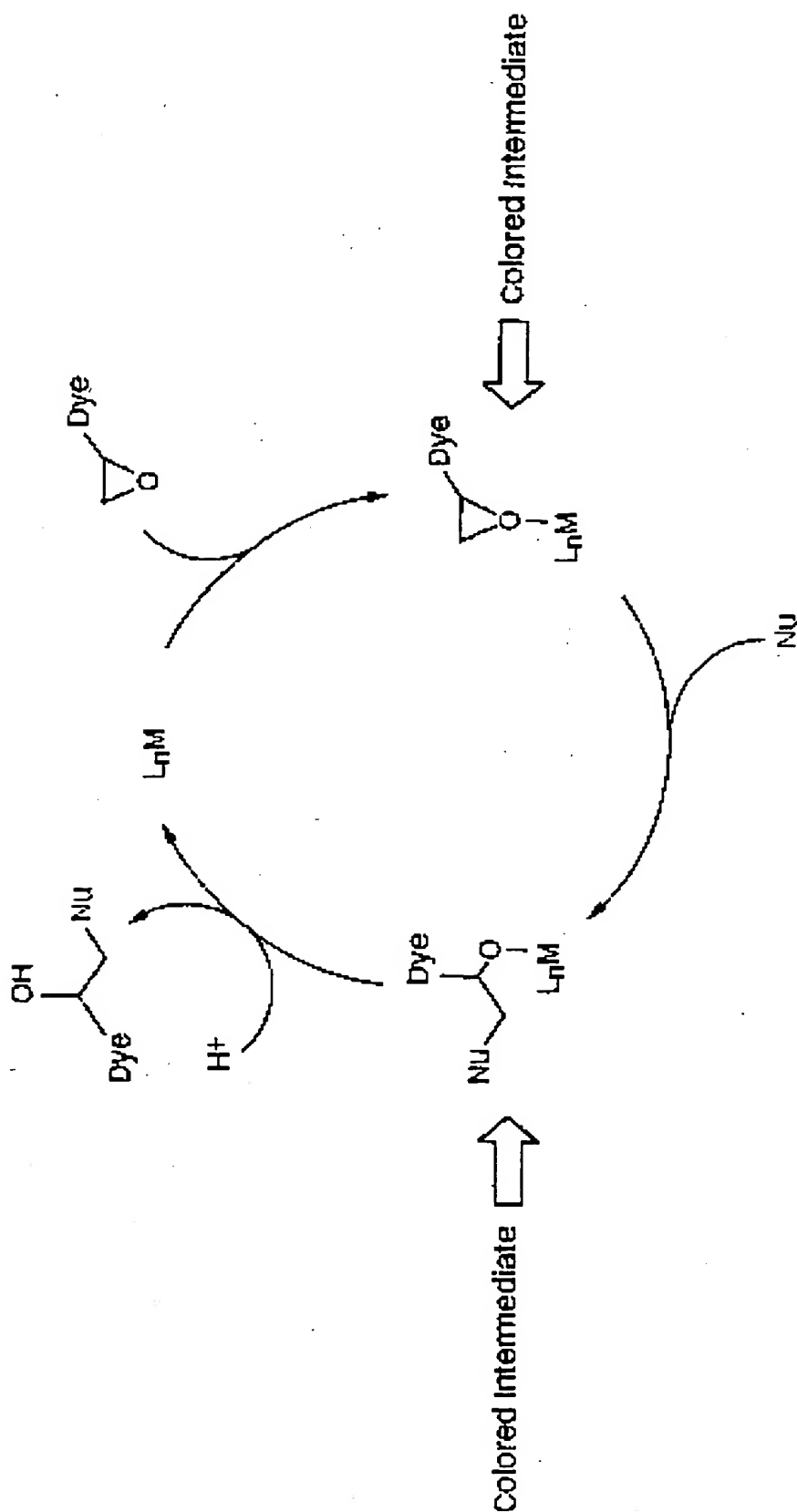
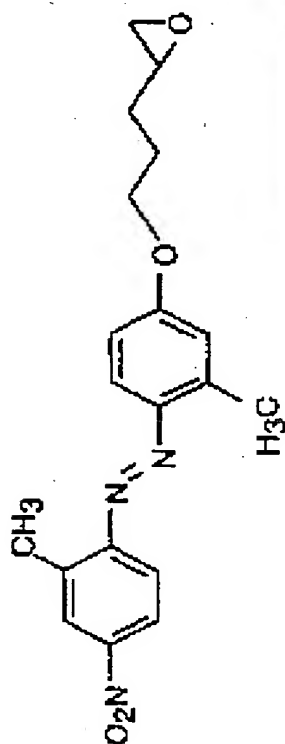
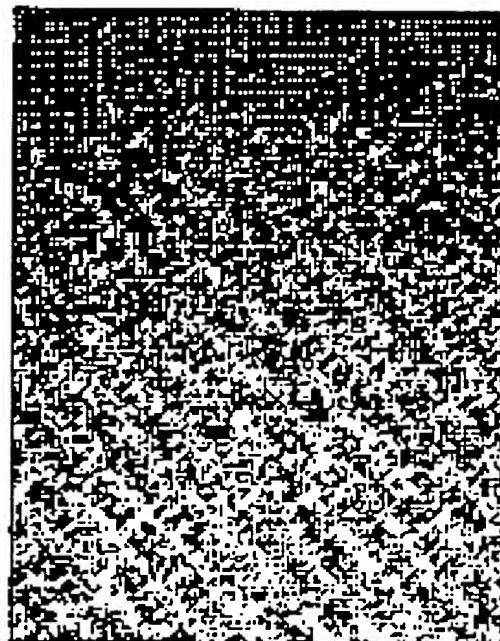
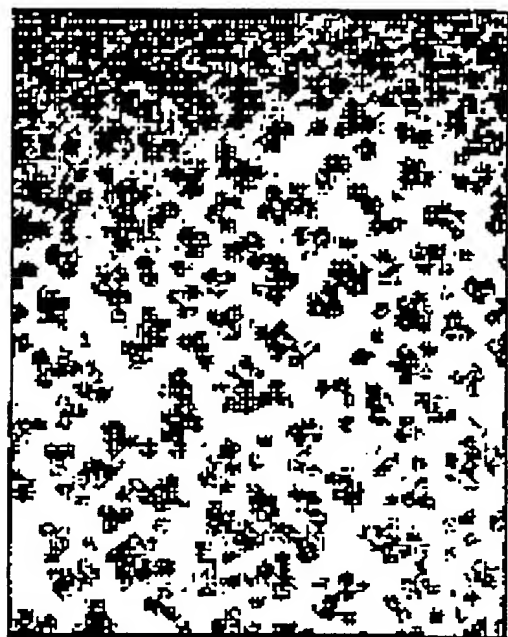


FIG. 11F

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0.2 M BnNH<sub>2</sub>  
DCE, 30 min

Yb(III) Library

0.2 M BnNH<sub>2</sub>  
DCE, 30 min

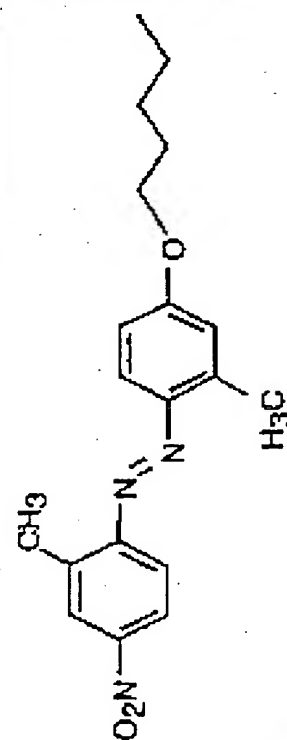
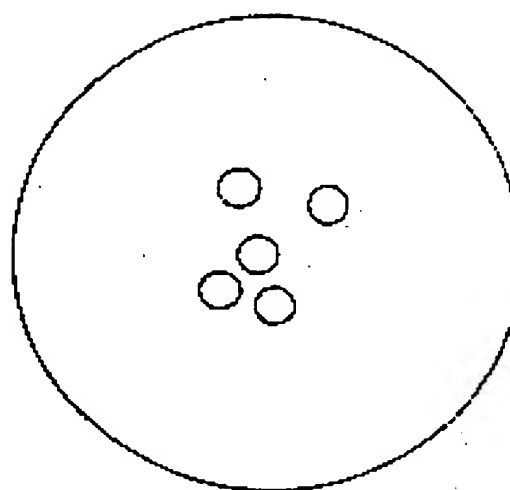
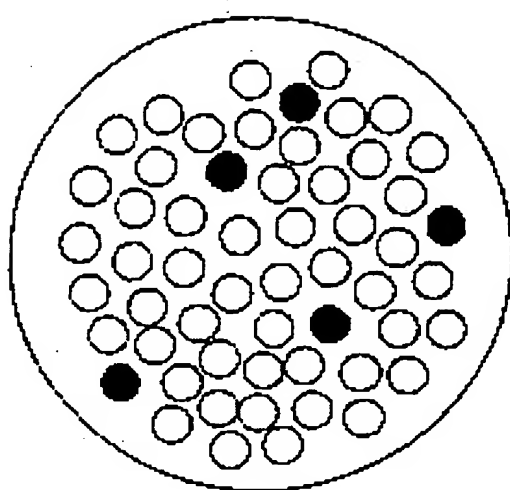


FIG. 11G

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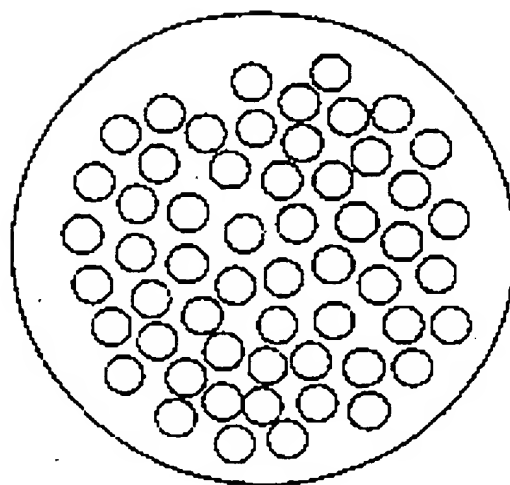


TLC of released compound  
shows starting epoxide.

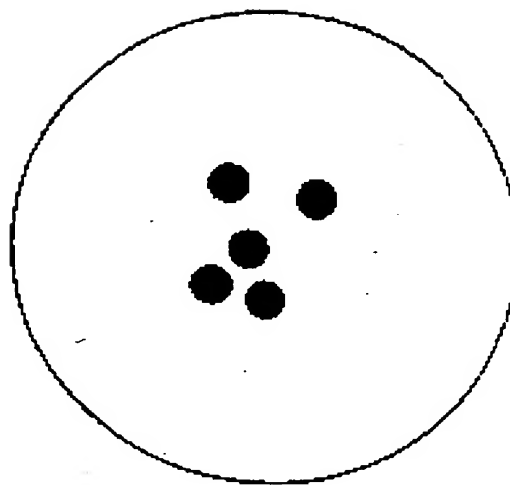


Amine

THF/Water

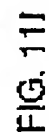


Yb(III)-Library



Red Beads Isolated

FIG. 11H



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Structure	Position 1	Turn Element	Position 2	End Cap
1	D-Ser	(S,S)-Cyp	D-Ser	Fur
2	L-Ser	(S,S)-Cyp	D-Ser	Pic
3	D-Ser	(S,S)-Cyp	D-Ser	Nap
4	L-Ser	(S,R)-Ind	L-Ser	Fur
5	L-Ser	Eth	D-Ser	Fur
6	L-Ser	Eth	L-Ser	Nap
7	D-Ser	L-Pro	D-Ser	Pip
8	D-Ser	(S,S)-Cyp	L-Phg	Acy
9	D-Ser	Eth	L-Phg	Acy
10	L-Ser	(S,S)-Cyp	D-His	Pic
11	L-Ser	L-Leu	D-His	Pic
12	D-His	(S,S)-Cyp	L-Ser	Pic
13	L-His	(S,S)-Cyp	D-Ser	Pic
14	L-Ser	Eth	D-Met	Pic

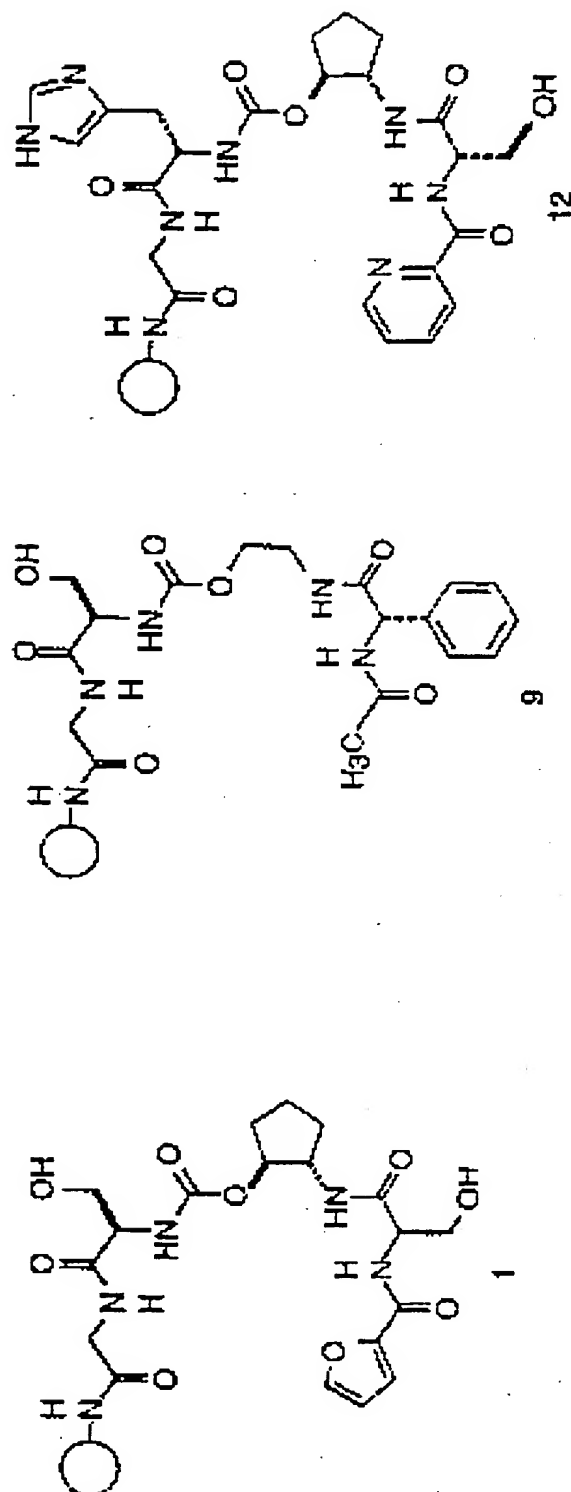


FIG. 11J

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